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GROSS AND HISTOLOGIC CHANGES IN THE KNEE JOINT IN RHEUMATOID ARTHRITIS

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In previous papers [1] we presented the gross and histologic changes that are observed in joints with advancing age and in certain infectious conditions. It was pointed out that the changes which occur with advancing age are identical with those which have been described repeatedly as being characteristic for degenerative arthritis. It was shown that in the different infections the type and extent of the joint lesions depend on the mode of infection; that is to say, on whether it starts as a metastatic synovitis or appears in the joint by extension from the bone marrow or from the exterior. Degenerative arthritis begins in the articular cartilage and involves the bone and occasionally the synovial membrane secondarily. On the contrary, in the infectious group the lesions begin most often in the synovial membrane, less frequently in the bone. In view of these findings the changes found in three cases of rheumatoid arthritis were studied to compare the lesions in this condition with those of degenerative and infectious arthritis. We obtained autopsies in two of the cases; in one the process was in a comparatively early stage; in the other, far advanced. The early case occurred in a patient who died from cinchophen poisoning, and for the material we are indebted to Dr. Timothy Leary. The material from the third case was obtained through the kindness of Dr. Tom K. Richards, who resected the knee joint of the patient.

REPORT OF CASES

CASE 1.—A white woman, aged 40, complained of arthritis of both knee joints and of the interphalangeal joints of both hands. This condition had bothered her at varying intervals for a period of two years. During the week before admission she took 30 capsules of cinchophen hydro-iodide and then hemorrhages appeared beneath the superficial layer of the skin of the face, about the ankles, wrists, legs,

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1. (*a*) Keefer, C. S.; Parker, F., Jr.; Myers, W. K., and Irwin, R. L.: Arch. Int. Med. **53**:325, 1934; (*b*) Arch. Path. **17**:516, 1934. (*c*) Keefer, C. S.; Parker, F., Jr., and Myers, W. K.: ibid. **18**:199, 1934.

arms and trunk. For two days before entry into the hospital there had been symptoms of a pulmonary infection with fever, cough and expectoration.

On examination the temperature was 103 F., the pulse rate 120 per minute and the respirations 45 per minute. There were extensive purpuric lesions over the face, arms, legs and trunk. There was no jaundice. The lungs showed evidence of bilateral bronchopneumonia, and the interphalangeal joints showed fusiform swelling and enlargement with some pain and tenderness on pressure and limitation of motion. The knees showed periarticular swelling and thickening without any excess accumulation of fluid. They were painful on motion and pressure. The red blood cell count was 4,447,000 per cubic millimeter; the hemoglobin, 50 per cent; the white blood cell count, 6,900. The urine showed slight amounts of albumin, an occasional leukocyte and a few red blood cells and granular casts. The bleeding time was 5.5 minutes (Duke) and the clotting time 2.5 minutes (capillary tube method), which is normal.

The clinical course was one of progressive failure with signs of bronchopneumonia, anemia and leukopenia with agranulocytosis. Death occurred three days after admission. The clinical diagnoses were: drug intoxication, bronchopneumonia, rheumatoid arthritis, agranulocytosis and secondary anemia.

The anatomic diagnoses were: dermatitis medicamentosa, purpura, organizing pneumonia and abscesses of the lung. The liver was normal on both gross and microscopic examinations.

Gross Examination of the Knee Joint.—The synovial membrane and articular surfaces of the right knee joint were removed for study. The examination of the gross specimen revealed the following features: The synovial membrane and the underlying connective tissue were increased in thickness. The surface was irregular, and the membrane projected into the joint cavity as long tags of tissue. Wherever there were depressions or erosions in the articular cartilage the synovial membrane had extended into them and attempted to fill the cavities. In several areas, especially over the posterior aspect of the lateral condyle of the femur, the synovial membrane had grown over the surface and had become adherent to it. The semilunar cartilages were difficult to recognize as separate and distinct structures owing to the great amount of synovial membrane that had overgrown and surrounded the cartilage.

The articulating surface of the patella showed fibrillation and erosion of the cartilage on the medial horizontal facets. About the edge the synovial membrane appeared in long thin tags, and over the median surface it was adherent to the cartilage. In the patellar groove of the femur the cartilage was irregular and fibrillated, and at the periphery the synovial membrane had grown over the cartilage. On the lateral condyle there was a small hole in the cartilage which communicated with a small cavity extending into the bone. Over a large area of the articulating surface of the medial femoral condyle there was a complete absence of cartilage, and the underlying bone contained several small holes communicating with the surface. The posterior part of the lateral condyle of the femur was covered with a thick layer of synovial membrane and was everywhere irregular. There were some areas of erosion of the cartilage and a small necrotic area in the underlying bone.

The articulating surface of the lateral condyle of the tibia showed extensive erosion and fragmentation of the cartilage. The synovial membrane had grown over the area of the condyle that was covered by the semilunar cartilage. There were irregularities in the articular surface and fibrillation of the cartilage in the vertical plane. The medial condyle showed extensive destruction of the cartilage with marked overgrowth of synovial membrane and small holes in the underlying bone.

Histologic Examination.—Microscopic examination showed the synovial membrane to be much thickened with an increased number of synovial cells (fig. 1). There were numerous vascular papillary projections, and in places there were areas of perivascular infiltration with lymphocytes and numerous multinucleated cells. Some of these papillary projections were necrotic. In some places both the papillary projections and the synovial membrane proper showed loss of synovial cells with a deposition of fibrin; in others, a meshwork of fibrin occurred between the synovial cells. In one section there were papillary projections of fibrin which showed beginning organization at their bases. In the subsynovial tissue there was a marked infiltration with lymphocytes, rare giant cells of the foreign body

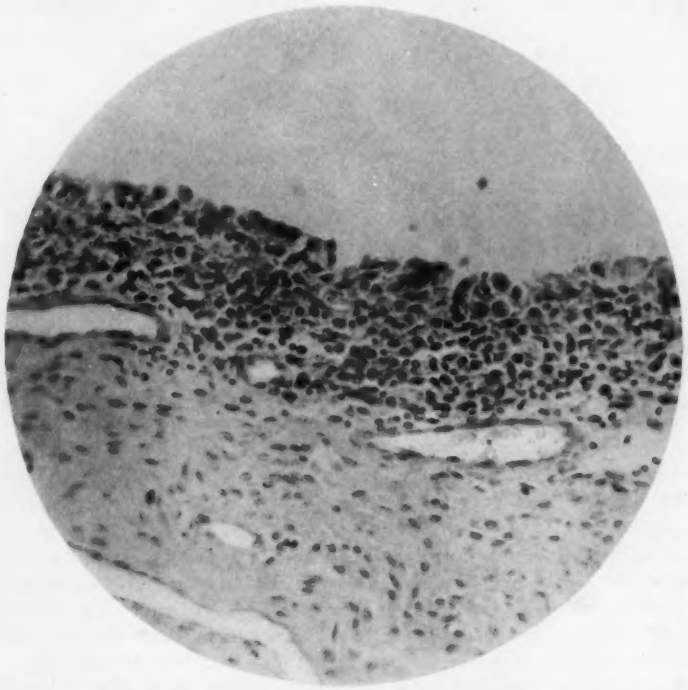

Fig. 1.—Section of synovial membrane (× 95) showing proliferation of synovial cells and infiltration with lymphocytes and plasma cells.

type and macrophages, some containing blood pigment. In the fat there was marked perivascular infiltration with lymphocytes. The striated muscle about the capsule showed degeneration and atrophy.

No bacteria were seen in the synovial membrane in sections stained by the Gram-Weigert method.

Sections from the cartilage and bone showed defects, fibrillation and thinning of the cartilage. The cartilage was necrotic in places, as was the underlying subchondral bone. In one area, the joint surface was composed of a layer of dense vascular connective tissue covered with synovial cells and infiltrated with lymphocytes and plasma cells—evidently an ingrowth of the synovial membrane from the periphery. Beneath this connective tissue the articular cartilage had for

the most part disappeared, leaving the subchondral bony plate impinging on the fibrous tissue layer. In a few places remnants of the cartilage could be made out, and these apparently were undergoing dedifferentiation into connective tissue. There were small cavities and multilocular cysts in the marrow. The cysts were filled with fatty macrophages and blue-staining granular material. The walls were made up of hyaline material and surrounded by connective tissue. In the region adjacent to the cysts there was a perivascular infiltration with lymphocytes, and the bone was in part necrotic. Osteoclasts were numerous in relation to both the degenerated and the living bone. The origin of this type of cyst was shown by some earlier lesions which consisted of necrosis of fat tissue, which was taken up by macrophages and then surrounded by connective tissue. The débris in some of the cysts consisted of small pieces of cartilage which were partly necrotic. They were surrounded by mononuclear and polymorphonuclear leukocytes. The connective tissue of the wall of the cavity was continuous with the connective tissue of the synovial tissue which covered the joint surface at this point.

In this case there were changes in the synovial membrane with signs of chronic inflammation, loss of cartilage with necrosis and cyst formation in the underlying bone. In the cartilage and bone there were many changes characteristic of degenerative arthritis. This was anticipated from our previous observations and the age of the patient. There were, however, changes in the synovial membrane and periarticular tissues which are not seen in degenerative arthritis but which are characteristic of rheumatoid arthritis.

Case 2.—A woman, aged 60, was admitted to the hospital on account of loss of memory and disturbed mental condition. An accurate history was not obtained but it was learned that she had been unable to get out of bed for five years preceding her death on account of severe chronic arthritis which had produced crippling.

On examination she was found to be underweight and emaciated. The mucous membranes were pale, and there were decubitus ulcers over the buttocks. There was a senile emphysema and râles at the bases of both lungs. The joints of the hands and feet, the ankles and the knees showed marked deformity and periarticular thickening. There was no anemia, but a moderate leukocytosis with the leukocyte count varying between 11,100 and 16,500 per cubic millimeter. On the second day after admission signs of bronchopneumonia appeared over the lower lobes of both lungs. Death followed ten days later.

The clinical diagnoses were: chronic bronchitis, emphysema, bronchopneumonia and chronic rheumatoid arthritis. The anatomic diagnoses were: bronchopneumonia, bilateral acute bronchitis, chronic arthritis (rheumatoid) of the wrists and knees, cardiac hypertrophy, old fibrous peritonitis and pleuritis.

Gross Examination.—The knee joints were opened and the articular surfaces and synovial membrane removed for study. The following observations were made on the gross specimens.

On opening the knee joints the periarticular tissue and synovial membrane were found to be greatly thickened. There was a moderate amount of thick exudate containing old blood pigment. Since both knee joints presented practically the same picture they are described together. The articulating surfaces of the

patellae were almost completely obscured by a great thickening and overgrowth of synovial membrane that had invaded the joint cavity from the periphery and had grown over the surface. The entire surface of the femoral condyles was greatly distorted and irregular. Here and there the cartilage and bone projected from the surface, leaving areas of elevation and depression. At no point was the surface smooth. The surface resembled a relief map of a very rugged country with many hills and valleys. In some areas there was great atrophy of the cartilage, and the superficial layers resembled fibrous tissue. At the edges the synovial tissue had invaded the joint cavity and covered the surface of the cartilage.

The articulating surfaces of the tibias were reduced in size and distorted. This was due to the great overgrowth of synovial membrane and fibrous tissue over the semilunar cartilages and the articulating surfaces. Indeed, the semilunar cartilages could not be recognized as distinct structures. The articular cartilage was thinned and irregular and replaced by fibrous tissue.

Histologic Examination.—The extent of the changes in the synovial membrane varied considerably from one portion to another. In the regions showing the least involvement the surface of the membrane was covered with delicate papillary projections made up of vascular connective tissue covered with flattened cells and containing occasionally a few lymphocytes. The deeper layers of the synovial sac showed a slight perivascular infiltration with lymphocytes and plasma cells. Where the process was more marked the synovial surface was thrown into folds and was covered with coarse villous projections. These had a central core of fibrous tissue, often dense and hyaline, and contained numerous blood vessels, often accompanied by a perivascular infiltration with many lymphocytes and plasma cells. The synovial cells covering these projections were large, their processes prominent, and they tended to have a palisade arrangement, lying with their long axes at right angles to the joint surface. In places these cells were covered with a delicate layer of fibrin; in other areas they had disappeared and there was present a dense layer of fibrin, often hyaline in character. The connective tissue wall of the synovial membrane was thickened and was infiltrated with numerous lymphocytes and plasma cells, most markedly in the vicinity of the blood vessels. Scattered here and there were histiocytes containing hemosiderin.

The articular surface was covered in great part by rather dense vascular connective tissue which presumably had grown in from the synovial membrane at the periphery, as no fibrosis of the marrow was present. Scattered along the surface also were projecting nodules of cartilage and these, as a rule, were not covered by the connective tissue. These cartilaginous nodules showed at their bases islands of vascular connective tissue with ossification proceeding at the peripheries of these islands. Only a few areas of articular cartilage of the usual type were present, and these showed varying degrees of fibrillation and, as a rule, islands of ossification at their bases. Beneath the connective tissue covering the articular surface there was a thin layer of bone, often containing islands of cartilage which represented remnants of the deep layer of the original articular cartilage. The line of the articular surface was markedly distorted, showing areas of flattening and also projecting areas due to the cartilaginous nodules mentioned.

The bony layer described as underlying the connective tissue in part represented the original subchondral bony plate. However, much of this bony layer was newly formed, since the original subchondral layer could be made out some 3 or 4 mm. beneath the surface. This construction of a new articular layer of bone has been described also in case 3. The process showed various stages.

Where it was complete, the original subchondral bone existed merely as a thin layer with an occasional island of cartilage embedded in it. Where it was somewhat more recent, the bone surrounded islands of cartilage and these were penetrated by vascular, ossifying tissue. In one area the articular cartilage, which still formed the joint surface, was being invaded at both sides by such ossifying tissue so that there was a definite narrowing at these regions, suggesting that eventually this mass of cartilage would be separated into two pieces with the portion toward the articular surface finally forming the new bone layer in that region, and the deeper portion representing the line of the original subchondral bony plate as described. In a region adjacent to this area, this separation had already taken place, the intervening spaces between the two portions being filled with trabeculae of bone and fatty marrow. The process of the formation of the new articular surface has been described in detail in case 3 and it does not seem necessary to repeat it here; the changes were identical. The bone of the epiphysis in general showed atrophy, the trabeculae being much thinner than normal and more widely separated. The marrow was fatty throughout and showed no pathologic changes.

The alterations in the joints of this patient were much more marked than were those in case 1. The duration of the disease and the disability caused by it were greater. There was extensive destruction of the cartilage in addition to the reaction in the synovial membrane. The atrophy of the bone was extreme.

CASE 3.—*Gross Examination.*—The specimen consisted of the articulating surface of the tibia and the posterior aspect of the condyles of the femur, which were resected.

About the borders of the specimens the synovial membrane was greatly thickened and showed proliferation of the synovial membrane and the underlying connective tissue. In some areas the synovial membrane had grown over the cartilage to which it was firmly attached. The cartilage over the area of the tibial condyle subjected to the greatest pressure showed thinning and erosion. Over other areas the cartilage was discolored, was definitely wrinkled and projected in an irregular manner. It was soft and had lost its normal elasticity. Some parts of the surface were distinctly nodular (fig. 3). These nodules were firm, were covered by a thin layer of cartilage and varied from 2 to 4 mm. in diameter.

Histologic Examination.—The surface of the synovial membrane was irregular and showed a considerable number of papillary projections made up of vascular connective tissue densely infiltrated with lymphocytes and plasma cells and covered with a layer of synovial mesothelium. The synovial surface elsewhere was in part intact and in part covered with a dense layer of fibrin with loss of the synovial cells. The intact synovial layer was made up in places of several layers of synovial cells, the processes of which were unusually prominent. In foci there was a thin layer of fibrin over the intact synovial membrane. Beneath the synovial cells, in the connective tissue, were numerous scattered lymphocytes, plasma cells, a few polymorphonuclears and multinucleated cells. The multinucleated cells had nuclei of equal size, often with a peripheral arrangement. The cytoplasm, which was acidophilic, contained numerous centrioles. These cells often showed several processes of considerable length; occasionally such a process extended up between the synovial cells to the surface. No foreign bodies could be detected

in their cytoplasm. Their exact nature was not clear. However, the type of nucleus and processes so closely resembled those of synovial mesothelium, and their close connection with the latter suggested that at least some of them, if not all, were of synovial origin. In the connective tissue beneath the region just described there were numerous large focal collections of lymphocytes and plasma cells and, in addition, in places there were macrophages containing hemosiderin. An occasional definite lymph follicle with an active germinal center could be found. The connective tissue of the capsule showed an occasional perivascular collection of lymphocytes. The capillaries beneath the synovial membrane were prominent, as were their lining endothelial cells. Elsewhere the blood vessels were not abnormal.

Only a small portion of the joint surface was covered with cartilage. This cartilage was thinner than normal, its surface was roughened with papillary projections which were often covered with fibrinoid material, and it tended to stain acidophilically. At its junction with the subchondral bony plate were several foci of vascular connective tissue which penetrated somewhat into the cartilage. The greater part of the articular cartilage had disappeared, and the joint surface was covered with a layer of rather dense connective tissue containing medium-sized blood vessels and infiltrated with numerous lymphocytes and plasma cells. This connective tissue layer was covered with synovial cells and was obviously an ingrowth from the synovial membrane. Where this connective tissue covered the articular surface no articular cartilage was present save occasionally a thin layer connected with the subchondral bony plate. Chondroid tissue and young cartilage could be found in connection with the subchondral plate and, in one area, embedded in the connective tissue layer.

As mentioned in the foregoing paragraph, the connective tissue layer was a continuation of the synovial membrane and was similar in structure. In places there were deposits of fibrinoid material on its surface, and here the synovial cells had disappeared. Its surface showed numerous coarse papillary projections extending for a considerable distance above the joint surface. In several places it had grown down through defects in the underlying bone into the marrow for a short distance.

The subchondral bony plate showed a variety of changes. In rare places it persisted with its normal cartilaginous component but was covered with the connective tissue layer. In other areas the plate and cartilage could be found but the cartilage was covered on the joint side by a closely applied layer of bone containing a few islands of connective tissue. Elsewhere the plate and cartilage could be distinguished, as before, with a bony covering on the joint side, but here there were bony projections also at right angles to the bony plate, extending toward the joint and terminating in another plate of bone parallel to the original subchondral plate. This new bone contained fatty marrow and also islands of connective tissue. The most exaggerated example of this picture was seen in one section in which the old subchondral plate could be distinguished in its entirety, but intervening between this and the joint cavity were bony trabeculae and fatty marrow for a distance of 2 mm., with a new plate of bone underlying the connective tissue lining the joint. In other areas the subchondral bony plate had disappeared entirely, leaving bony trabeculae running approximately at right angles to the joint surface, which was covered with connective tissue. In a few places where small breaks in the plate were present the fibrous tissue from the articular surface had penetrated down into the marrow. Nodules of chondroid tissue were found projecting from the surface of the bone in the region of the subchondral plate. In one focus where the articular cartilage had been lost, leaving the underlying bone exposed, there were marked thickening of the bone

extending down for quite a distance and fibrosis of the marrow. As a result of these various changes the joint line was markedly irregular. The bony trabeculae of the epiphysis seemed thinner and more widely separated than normal.

There were a few scattered areas of normal hematopoietic tissue in the marrow. As described in the foregoing paragraph, invasion of the marrow by fibrous tissue from the articular surface had occurred in several areas. Also fibrosis of the marrow had taken place where there was marked thickening of the bone beneath regions where the articular surface was denuded. In connection with the latter, large focal collections of lymphocytes were found in the marrow spaces.

In this case, as in case 2, extensive alterations were found in the synovial membrane as well as in the articular cartilage.

COMMENT

From these three cases it is evident that the constant lesion is in the synovial membrane and periarticular tissues. The other changes are secondary. Following the synovitis a series of changes take place that require study and analysis. They will be presented but before that is done it will be well to summarize the knowledge of the synovial lesions which are characteristic of the disease.

The first change observed in the synovial membrane is an increase in the number of synovial cells with marked thickening of the membrane. Here and there the synovial cells are destroyed and become covered with fibrin. In the synovial tissue there are collections of lymphocytes and plasma cells, macrophages and rare giant cells. These various cells collect in dense foci arranged about blood vessels in some areas and not in others (fig. 2). In the fat of the periarticular tissues there is an infiltration of lymphocytes about the blood vessels. The striated muscle about the capsule of the joint shows degeneration and atrophy. Following the proliferation of the synovial membrane and its overgrowth onto the surfaces of the joint, the articular cartilage frequently disappears. This has been ascribed by Nichols and Richardson [2] and Allison and Ghormley [3] to a dual process. They maintain that as the synovial membrane passes over the articular cartilage it becomes adherent to it and finally destroys it. At the same time they describe proliferation of connective tissue in the subchondral spaces with an invasion and destruction of the cartilage.

From our observations on the disappearance of the articular cartilage we have come to the conclusion that it takes place as a result of a solution of the cartilage under the connective tissue that has grown onto the articular cartilage and by a dedifferentiation of cartilage into connective

2. Nichols, E. H., and Richardson, F. L.: J. M. Research **21**:149, 1909.

3. Allison, N. A., and Ghormley, R. K.: Diagnosis in Joint Disease, New York, William Wood & Company, 1931.

tissue. We have not been able to convince ourselves that proliferation of connective tissue in the marrow of the epiphysis is a necessary and essential part of the pathologic process.

The foregoing statements are based on the following observations: When the cartilage under the connective tissue preserves the original characteristics of normal articular cartilage it appears to undergo solution. As a general rule, however, the cartilage beneath the connective tissue is quite different in appearance from normal articular cartilage.

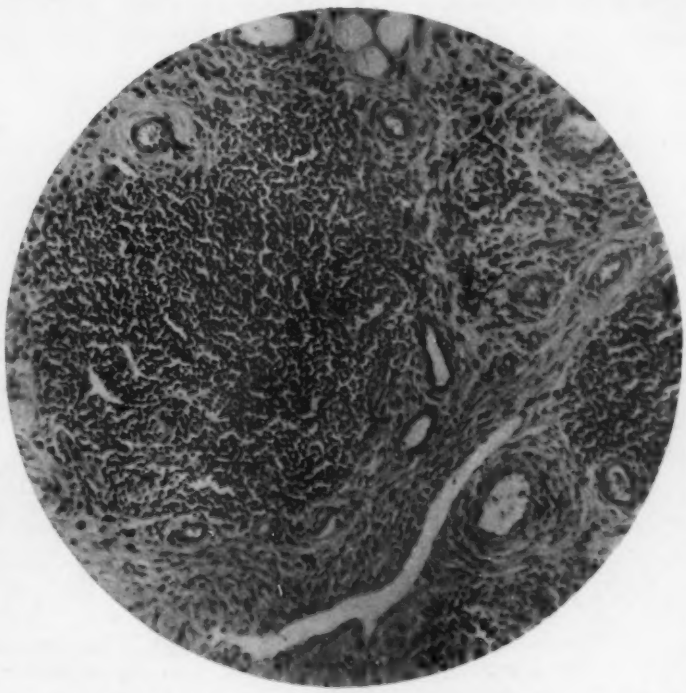

Fig. 2.—Section from subsynovial tissue showing infiltration with lymphocytes in foci about blood vessels and elsewhere (× 125).

The intercellular substance stains with acid dyes; the cartilage cells no longer occur in groups but tend to become more separated and to have a clear zone about them. All of these changes are more marked the nearer the overlying connective tissue is approached. The other process that takes place is a conversion of the cartilage into connective tissue. This was exceedingly common in the cases herein described. In numerous sections it was found that cartilage was being converted into connective tissue, since young cartilage cells could be traced into the connective tissue where they became still more widely separated and more irregular in shape.

Since the cartilage seemed to change into connective tissue so frequently the question arose whether this ever occurred without evidence of connective tissue growing over the surface of the articular cartilage. We have many sections bearing on this question, and it can be stated that it was not observed. There were some sections in which this apparently was not true, and they require comment. In a few sections, nodules of cartilage were seen projecting upward from the surface of the joint and they were uncovered by connective tissue, although connective tissue could be seen surrounding and between them (fig. 3). The explanation of these nodules was that they represented a formation of

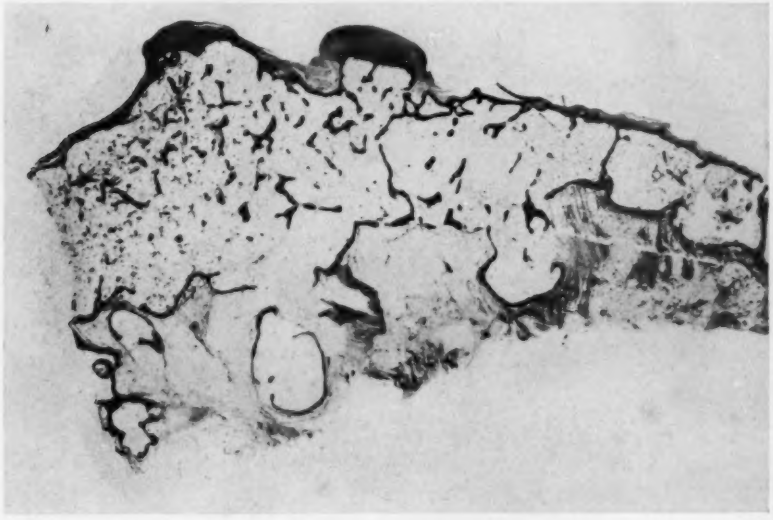

Fig. 3.—Section showing small nodules of cartilage projecting upward from the surface of the joint. They have been formed from the connective tissue which at one time covered the whole surface of the joint (× 4).

cartilage from connective tissue which at one time covered the whole surface area. That this can occur there can be no doubt since in figure 4 it is seen that cartilage, bone and a new articular surface have been formed on top of old articular cartilage and this, in turn, is covered by connective tissue. In other words, when connective tissue grows over articular cartilage the latter either undergoes solution or becomes changed into connective tissue. The connective tissue which grows over the surface of the joint is also capable of forming new cartilage and finally bone.

In sections which failed to show any connective tissue growing over the surface of the joint there was no evidence of cartilage changing into

connective tissue and no marked proliferation of the connective tissue of the marrow. This was demonstrated clearly in a cross-section of the tibia. At the periphery of the joint surface the articular cartilage was covered by connective tissue and beneath it the cartilage was undergoing dissolution. The part of the cartilage which showed no connective tissue over its surface was normal in appearance except for the presence of fibrillation, an associated lesion due to degenerative changes.

The articular cartilage was destroyed in still another way. We have described the irregularity of the surface of the joint in these cases and have shown that this irregularity is due to a replacement of the articular cartilage by new cancellous bone, so that the surface consists of a very thin layer of bone, connective tissue or cartilage (fig. 5). The remains

Fig. 4.—Section showing the original articular cartilage covered by connective tissue, new cartilage and bone. There is also evidence of destruction of part of the original articular cartilage with new bone formation (× 3).

of the old subchondral joint line are seen several millimeters below the surface. The formation of this double line with cancellous bone intervening has been explained by some to be due to a proliferation of the perichondrium of the articular surfaces. The existence of perichondrium in adult cartilage can be doubted since there is very little evidence to show that it exists and we have never been able to detect tissue that could be differentiated as perichondrium in the joints which we have examined. We believe, however, that the appearance of a double line and the destruction of the cartilage can be explained on another basis; namely, that it results from a replacement of the articular cartilage by cancellous bone, and it progresses not from the subchondral plate by ingrowth of connective tissue into the cartilage but begins at the periph-

ery of the joint and spreads through the central portion of the articulating cartilage. In some sections one can trace the process from both ends. This is illustrated clearly in figure 6. As it progresses the subchondral bony layer becomes separated from the superficial layers of cartilage, and gradually the whole articular cartilage may become ossified and only remnants of the old subchondral line will be seen. That this process does not progress from below upward was confirmed by other sections in which the cartilage was being destroyed from the side and from the articular surface downward by ossification.

It seems clear, then, that the double line of cancellous bone results from the ossification of the articular cartilage, and that this is accomplished by an ingrowth of ossifying tissue from the periphery of the joints.

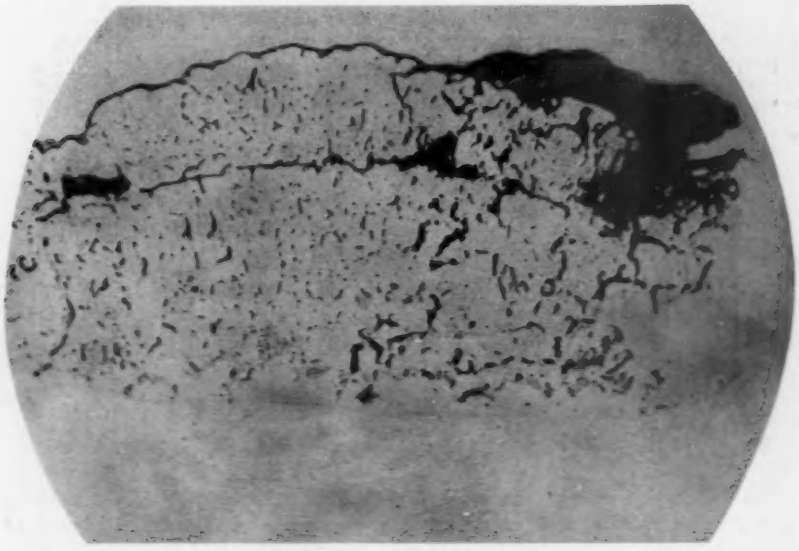

Fig. 5.—Section of the femoral surface of the knee joint showing complete ossification of the articular cartilage and the remains of the original subchondral line (× 4). This is the end-stage of the process shown in figure 6.

There remains for discussion the question of the destruction of the cartilage by ingrowth of connective tissue from the epiphyseal marrow. In our previous paper [1a] on the histologic changes in the joints with advancing age we called attention to the occurrence of fibrosis of the marrow especially when the cartilage on the surface had been destroyed. This increase in connective tissue of the marrow extended up to and over the affected surface, and we interpreted this reaction as an attempt to repair the defect.

It was shown further that when the subchondral zone showed increased vascularization, a process which is common and which is pathognomonic of degenerative arthritis, occasional islands of vascular connective tissue extended upward into the overlying cartilage, and new bone formation took place about them. It is necessary, then, to take these findings into consideration when interpreting the changes that are seen in rheumatoid arthritis.

In many sections from these cases of rheumatoid arthritis it was demonstrated that the connective tissue that had grown over the surface of the joint frequently extended downward into the marrow after the cartilage and bone had been destroyed. This is seen in fig. 7. In these

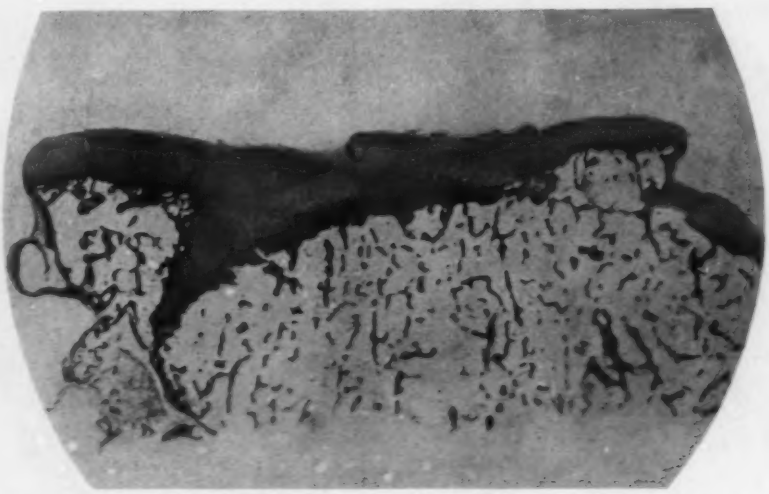

Fig. 6.—Section of the femoral surface of the knee joint showing ossification of the articular cartilage by a process progressing from the periphery of the joint (× 3).

cases the connective tissue on the surface was always older in appearance than that seen in the marrow, and it could be traced from the surface into the marrow. The evidence was not convincing that any great amount of destruction took place by invasion of the subchondral plate by connective tissue from the marrow, so that we did not feel that this was of fundamental importance in the pathologic process.

In summary, then, it can be reasonably maintained that destruction of the articulating cartilage takes place by solution and by dedifferentiation of cartilage into connective tissue once its surface has been covered with connective tissue. Secondly, it is replaced with cancellous bone by a process of ossification from the periphery. The destruction of carti-

lage by connective tissue growing into the cartilage from the subchondral spaces is minimal and not a fundamental pathologic process in the disease. It is seen when new bone formation goes on in such areas.

Changes in the Bone.—One of the outstanding features in these cases is the extreme degree of atrophy of the bone (fig. 5). It is demonstrable by x-ray film during life, and when one examines the

Fig. 7.—Section of a joint showing disappearance of the articular cartilage following an overgrowth of connective tissue. In one area the connective tissue proliferation has extended into the marrow from above (× 36).

bone histologically there is an amazing degree of such atrophy. The bone is reduced to a thin network resembling the finest lace. There is no evidence from the cases we have studied that the thinness of the bone is due to any process other than atrophy. That is to say, there is no indication of active bone destruction. We attribute this atrophy to disuse and not to a pathologic process causing dissolution of bone.

From the foregoing discussion there is justification for the belief that the fundamental process in rheumatoid arthritis is an inflammatory process in the periarticular tissues and synovial membrane. The other anatomic changes are secondary to this essential change, that is to say, the destruction of cartilage, the atrophy of bone and new bone formation. A part of the process can be explained on the basis of disuse of a joint together with the loss of cartilage that occurs following the connective tissue overgrowth. We emphasize this point in order to call attention to the fact that any theory that attempts to explain the pathogenesis of rheumatoid arthritis must take into account the mechanism by which the changes in the periarticular tissues come into being. The general pathologic changes are summarized in the table.

Pathologic Lesions in Rheumatoid Arthritis

Primary	Secondary	Miscellaneous
Synovitis	Destruction of cartilage	Lymphoid hyperplasia
Periarticular change with and without subcutaneous fibroid nodules	Atrophy of bone	Calcification of blood vessels
	New bone formation	Amyloidosis
	Subluxation	Disturbances of growth
	Ankylosis (fibrous, bony)	Pigmentation of the skin
	Muscular atrophy	

The lesions in the cartilage which are so distinctive of degenerative arthritis are quite different from those resulting from destruction of the cartilage by overgrowth of connective tissue. We make this statement and emphasize it since it has been alleged with some confidence that both degenerative and rheumatoid arthritis [4] result from the same underlying cause or group of causes. The origin of this view has as its basis the clinical observations that many patients with rheumatoid arthritis show degenerative changes in the cartilage. This is true but not surprising since a high percentage of persons after 40 years of age show degenerative changes in their joints. If rheumatoid arthritis develops after degenerative lesions are present, and this is not uncommon, then it naturally follows that the pathologic lesions of both conditions will be present together. Any one who has had the opportunity to study the gross and the histologic pictures of degenerative and rheumatoid arthritis cannot question that the underlying mechanisms in the two conditions are quite different. The picture of each is highly characteristic and can be recognized readily with a little experience. It is necessary to make the distinction since without it misunderstandings arise.

4. Archer, B. H.: J. A. M. A. **102**:1449, 1934. See this paper for additional references to articles suggesting the unitarian theory.

SUMMARY

Gross and histologic examinations of the tissues from three cases of rheumatoid arthritis were made. The following points were brought out:

In rheumatoid arthritis the primary and essential lesion of the joint is an inflammatory reaction in the synovial membrane and periarticular tissues. The other changes are secondary to this process.

The articular cartilage disappears as a result of an overgrowth of connective tissue on its surface, dedifferentiation into connective tissue and ossification of the articular surface.

The atrophy of bone is not due to active bone destruction. It is dependent, we believe, on disuse and there is a loss of calcium in the bone which accounts for it. We suggest that this is the result of disuse.

The lesions of rheumatoid arthritis are easily distinguishable from those caused by degenerative changes and those resulting from infection of the joints with micro-organisms.

The theory that degenerative and rheumatoid arthritis result from the same underlying factors is untenable.

DIFFUSE CORTICAL CONTUSION OF THE OCCIPITAL LOBE

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LOS ANGELES

Contusion is one of the more common traumatic lesions of the brain. While there is some difference of opinion as to the exact mechanism of its production, it is quite generally agreed that in most instances it is a contrecoup and not a direct effect of the injury. Two notable exceptions are those cerebral contusions which occasionally result from depressed fractures of the cranial vault and cerebellar contusions secondary to linear fractures of the occipital bone which usually run near or into the foramen magnum.

There is a great variation in the size and character of cortical contusions. This variation is due to a number of factors: the size, shape and force of the traumatizing object, the mechanism and direction of its application to the head, and the peculiar anatomic characteristics of the region opposite to the point of impact. With few exceptions, contusions are the result of one type of mechanical force—the head in motion strikes a solid and relatively stationary object. They occur typically as the result of traffic accidents, either when one automobile collides with another or with some stationary object or when a pedestrian is struck by a moving vehicle.

The size of the contused area probably depends on the intensity of the applied force. The extremely severe contusion which results fatally within from twelve to twenty-four hours is often very extensive, affecting the opposite temporal and frontal lobes and extending deeply into the underlying white substance. On the other hand, the contusion may be microscopic in size, evidenced only by tiny hemorrhagic effusions in the affected cortex.

The nature of the contusion depends largely on the anatomic relationship of the brain to the internal contour of the skull in the region. The shape of the contusion is also affected somewhat by the internal structure of the brain, particularly by the arrangement of the bundles of white fibers in the affected part. Three anatomic types of contusions are thus produced, the first with two subtypes: (1) the wedge-shaped temporofrontal contusion with (*a*) subfrontal and (*b*) anterolateral temporal subtypes, (2) the patchy and superficial dorsolateral contusion usually found in the opercular cortex and (3) the diffuse cortical contusion of the occipital lobe.

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It is the purpose of this study to draw attention to the essential features of the third type of contusion, which has not been described in the literature so far as I can discover. Certainly it must be familiar to coroner's pathologists in large metropolitan centers, but writers on the subject have not distinguished it from other types of cerebral contusions. The lesion appears as a diffuse reddish-brown discoloration of the involved convolutions. This coloration is due to the presence in the cortex of myriads of petechial hemorrhages. The lesion has been found invariably in the posterior portion of the cerebral hemisphere. The area involved varies considerably in size, from small patches of discoloration of the cortex, often at the depth of a sulcus, on the one hand, to a change in the cortex of the entire occipital lobe, on the other.

This study is based on observations in 8 such cases. The patients died after intervals of varying lengths in the Los Angeles County General Hospital, and the autopsies were performed by the coroner of the County of Los Angeles. The specimens were studied more in detail in the Cajal Laboratory. During the two and a half year interval during which the studies were made, a series of 241 specimens showing evidence of cerebral injury have been examined. Of this number 172 were found to show contusions of the brain. According to these figures, this type of lesion occurs in about 3 per cent of all cases of craniocerebral injury and constitutes only 4 per cent of cerebral contusions.

REPORT OF CASES

Case 1.—During an epileptic seizure a 57 year old man sustained an injury to the right side of the head in the frontal and parietal regions. He was admitted to the Los Angeles County Hospital on Jan. 24, 1933. He was uncooperative and was discharged against advice on the following day. He complained of right-sided headaches for several days but did not seek medical attention. On February 2 he became mentally hazy, was unable to talk and soon lapsed into a comatose state. He was readmitted to the hospital on February 3.

He was found to be rather stuporous, reacting to painful stimuli with movements of the extremities of the right but not of the left side. The head was deviated to the left. The pupils were unequal, the left being larger than the right; both failed to react to light. There was marked spastic paralysis of the extremities of the left side. A hemorrhage in the interval being suspected from the history, a left subtemporal decompression was performed. A large amount of subdural blood clot was evacuated. He died with signs of bronchopneumonia on February 4, a few hours after the operation and ten days after his injury.

The autopsy was made by Dr. A. F. Wagner, who permitted a further study to be made of the cerebral lesions in the fixed specimen. A linear fracture was found in the right parietal region which extended into the squamous portion of the right temporal bone. The remains of an extensive subdural hemorrhage were found over the dorsolateral surface of the left cerebral hemisphere, the clot being thickest toward the base. The hemorrhage was found to have its source in an extensive laceration of the basilar surface of the left temporal lobe. There had

been a rupture of a large intracerebral hemorrhage through the cortex. A large cavity had been excavated in the central portion of the left temporal and occipital lobes.

The cortex of the entire occipital lobe had a peculiar plum color. The margins of the area were rather sharply defined. Over the crest of the convolutions the pia-arachnoid had been torn as though by a swelling of the cortex. The extent of this discoloration of the cortex is shown in the accompanying drawing (fig. 1). On cut section the discoloration appeared at first to be limited to the cortex, but on closer study petechial hemorrhages were also observed in the subcortical white substance, which in some areas was softened and slightly discolored. In some regions the cortex seemed to be detached from the underlying white substance.

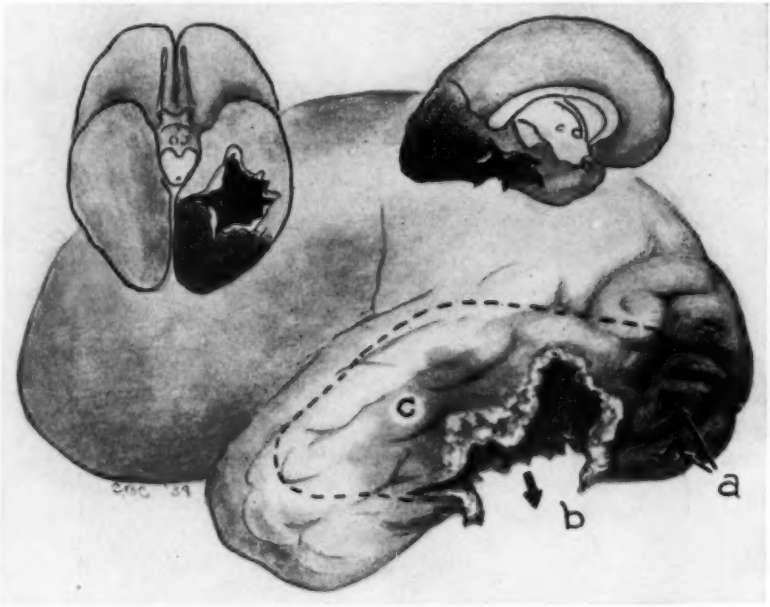

Fig. 1 (case 1).—A drawing showing the location and extent of the diffuse contusion: (*a*) ruptures of leptomeninges over convolutional ridges; (*b*) a laceration resulting from the rupture of an intracerebral hemorrhage through the cortex; (*c*) area within broken lines showing extent of intracerebral hemorrhage.

Comment.—There are several points of interest in this case which need to be stressed. While not germane to the problem at hand, the occurrence of an intracerebral hemorrhage so many days after injury and with the so-called "latent interval" calls attention to the possibility of such a lesion simulating an extradural or a subdural hemorrhage. This case is also of interest in that the cortex of practically the entire left occipital lobe was involved by the diffuse contusion, the most extensive lesion of the series.

CASE 2.—A 46 year old white woman was rendered unconscious as the result of an automobile accident on June 5, 1934, and was admitted to the hospital in a state of shock several hours thereafter. When examined at this time she had partially regained consciousness. A laceration 10 cm. long was found in the right parietal region, another 6 cm. long was present over the vertex, and still another 4 cm. long was located in the left temporal region. There were a few other superficial bruises of the skin of the extremities. No localizing signs suggestive of a focal cerebral lesion could be made out. She remainded in a semistuporous state and died with symptoms of bronchopneumonia twelve days after her injury.

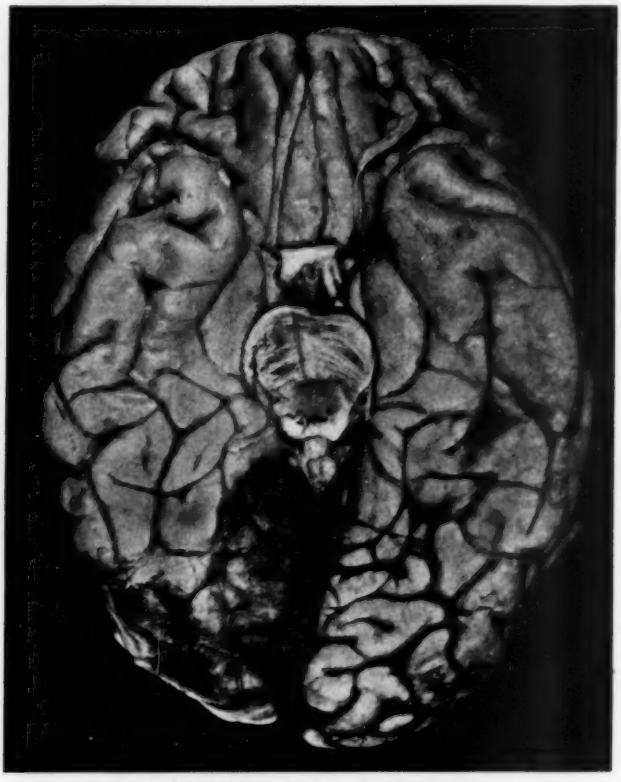

Fig. 2 (case 2).—Extensive diffuse contusion of the basilar surface of the temporal and occipital lobes.

At autopsy no fracture of the skull was found. There was a small amount of blood in the subarachnoid space in the right and left parietal regions, more on the left. There was a small contusion of the basilar surface of the left temporal lobe and others on the superior surface of the underlying cerebellum, that on the right being most extensive. A large portion of the basilar and medial cortex of the right occipital lobe presented the characteristic appearance of a diffuse cortical contusion (fig. 2). The occipital pole and a small portion of the dorsolateral surface of this lobe were similarly affected. A few scattered petechial hemorrhages were also found in the centrum of the anterior portion of the left frontal lobe.

Comment.—The extensiveness of the diffuse occipital contusion in this case is of special interest, particularly in view of the fact that the patient lived so long. Another interesting observation was the occurrence of the contusion of the superior surface of the underlying cerebellum. Such an occurrence is most unusual even in a large series of specimens presenting injuries.

In the following cases the cortical contusion was less extensive and only the essential points in the pathogenesis and pathology of the condition will be mentioned.

Case 3.—A 72 year old man died eleven days after being run down by an automobile. He was only slightly stuporous after his injury but became more so as time went on. A contusion of the right side of the head was found on examination. At autopsy there was observed a transverse linear fracture of the right temporal bone extending across into the middle fossa of the skull with local subdural hemorrhage. There was a severe contusion of the basilar surface of the left temporal lobe with local subdural hemorrhage. Petechial hemorrhages were present in the centrum of the right temporal and parietal lobes. Two small patches of diffuse contusion were noted (*a*) about the posterior end of the left superior temporal gyrus and (*b*) about a sulcus along the inferolateral margin of the occipital lobe.

Case 4.—A 63 year old man died twelve and one-half days after an assault by robbers. Following the injury there was bleeding from the right ear. After a short period of unconsciousness he recovered sufficiently to return to his work in spite of severe left-sided headaches. Ten days after the injury he became comatose and was admitted to the hospital for study. He died after a bilateral subtemporal decompression and partial evacuation of a left subdural hemorrhage. At autopsy no fracture of the skull was noted, but the remains of a subdural hemorrhage were found on the left side, together with a severe contusion of the medial part of the basilar surface of the left temporal lobe. Focal hemorrhages were also found in the right midbrain and in the pons. There was also a diffuse cortical contusion along the calcarine fissure on the left side.

Case 5.—A 60 year old man survived injuries resulting from an automobile accident for four and one-half days. He was unconscious for a short while, after which his mind was lucid for two days. During this time paralysis of the left arm was noted which was due to a fracture dislocation of the fourth and fifth cervical vertebrae. At autopsy, in addition to the fracture of the spine and injury of the cervical cord, a left subarachnoid hemorrhage and petechial hemorrhages in the left parieto-occipital centrum were found. A diffuse cortical contusion was also noted about the collateral fissure of the basilar surface of the left temporal and occipital lobes. There was no fracture of the skull.

Case 6.—A 41 year old man who fell from a moving automobile survived his injury for eight hours. After admission to the hospital on Dec. 12, 1933, he was found to have spastic left hemiplegia. There was a laceration of the scalp in the occipital region. At autopsy a basal fracture of the skull and a severe contused laceration with hemorrhage into the left temporal lobe were found, associated with some local subdural hemorrhage. There was also a marked edema of the right temporal lobe resulting in herniation of the hippocampal gyrus through the

incisura of the tentorium with consequent compression and distortion of the midbrain. The cortex lateral and caudal to the herniated hippocampal gyrus disclosed the typical changes of diffuse cortical contusion.

CASE 7.—A 53 year old man sustained an injury to the head in an unknown fashion during a brawl on April 20, 1935. He was admitted to the hospital the following day because of persistent stupor. Examination disclosed a bruise over the vertex of the scalp, rigidity of the neck and equivocal plantar reflexes but no evidence of motor weakness or inequality of the deep reflexes. The patient remained in a semicomatose state and died eleven days after his injury. At autopsy a contusion of the scalp over the vertex was found but no fracture of the skull. A moderate left subdural hemorrhage, a minor right subarachnoid hemorrhage and severe contusions of the basilar surfaces of both frontal lobes and of the left temporal and parietal lobes were also found. A diffuse contusion had discolored the cortex on the medial and basilar aspects of the left occipital lobe as well as along the right calcarine fissure.

CASE 8.—A 42 year old man was struck by an automobile while crossing the street on April 9, 1935, and was unconscious thereafter for a period of from fifteen to twenty minutes. He was admitted to the hospital the following day complaining of headaches. Evidences of bleeding from the right ear were found. He vomited repeatedly and was restless. Because of increasing drowsiness and dilatation of the right pupil a decompression of the right side was performed and a large subdural blood clot partially evacuated. Death ensued a few hours after operation and thirty-two hours after his injury.

At autopsy there was found an extensive linear fracture of the right side of the vault of the skull which extended into the base and a bruising of the right side of the scalp and the right temporal muscle. The remains of a very large right subdural hemorrhage were also found. There was a contusion of the tip of the right temporal and another of the dorsolateral surface of the left temporal lobe. A diffuse contusion of the cortex was found along the margin of a herniation of the right hippocampal gyrus into the incisura. This contusion also extended back along the calcarine fissure on this side. An old contusion of the cerebellar cortex was also noted, the result of a fracture of the occipital bone sustained five and a half years before.

PATHOGENESIS OF DIFFUSE OCCIPITAL CONTUSION

From a study of the clinical history and the observations at autopsy in this series of cases certain conclusions may be drawn as to the mechanical production of this type of lesion: Diffuse occipital contusion is found in persons over 40 years of age and usually after an interval of several days (exceptions: cases 6 and 8). It occurs after blows to the head, after falls and after automobile accidents. It may occur without fracture of the skull, and when fracture is present there is no definite anatomic relationship between it and the contusion.

In order that the mechanism of the production of diffuse contusion may be understood two important observations should be mentioned: This type of contusion invariably occurs in the posterior portion of the cerebral hemispheres and is usually confined to the occipital lobe. The scalp wounds are likewise found over the posterior one-half of the head.

The first observation suggests that some regional anatomic peculiarity is responsible for this type of lesion. The absence of superficial lacerations of the cortex in the affected area such as occur when the bruise is due to contact with bone and the occurrence of such lesions along the free margin of the tentorium suggest, furthermore, the possibility that the arrangement of the dural reduplications may play an important rôle in the production of the diffuse contusion. This is also suggested by the fact that in most instances the contusion is in the cerebral cortex adjacent to one of these dural reduplications (exception: case 1, in which contusion was associated with and evidently due to an extensive intracerebral hemorrhage).

In an attempt to evaluate the mechanical factors involved two possibilities must be considered: A primary type of lesion is apparently due to injuries sustained while the head is in motion, as is the case with other contusions. The contusion occurs predominantly, if not invariably, on the same side of the brain (cases 2, 3 and 5). When the vertex of the skull is injured primarily, both sides of the brain may be contused (case 7). A secondary type of contusion results from persistent pressure of the affected area against a dural reduplication, the pressure resulting from edema of one hemisphere (case 6), intracerebral hemorrhage (case 1) or subdural hemorrhage (cases 4 and 8). The lesion then occurs on the side affected by the cause of the pressure. The side so affected is not necessarily the side of the head originally injured.

The primary type of lesion is apparently produced by a sudden obstruction of the afferent veins of the cortex and subcortex or occlusion of these channels; the secondary type, by long-continued pressure against the relatively elastic dural reduplications. In the primary type the contusion is due to a sudden distortion of the occipital lobe on the side of the injury within a chamber the walls of which are formed in part by the smooth-surfaced dural reduplications (falx, tentorium). The occipital lobe is thrown against these reduplications and a contrecoup results. The relative elasticity and smoothness of these walls account no doubt for the absence of gross disorganization of the cerebral cortex common in other types of contusions. The sudden reversal of the current in the venous channels very likely accounts for the rupture of cortical and subcortical vessels and the formation of myriads of cortical and subcortical hemorrhages. Because of this interference with the circulation, softening of the cortex and underlying white substance ultimately results. The quantitative variation in the blood supply of the gray and white matter probably accounts for the difference in degree of softening and for the tendency for the cortex, after a short interval, to become separated from the underlying white substance.

PATHOLOGIC ANATOMY OF DIFFUSE CORTICAL CONTUSION

Diffuse contusion is found only in the occipital lobe or its immediate environs. It varies in extent from a small discolored area usually situated about the depth of the sulcus in one case to involvement of

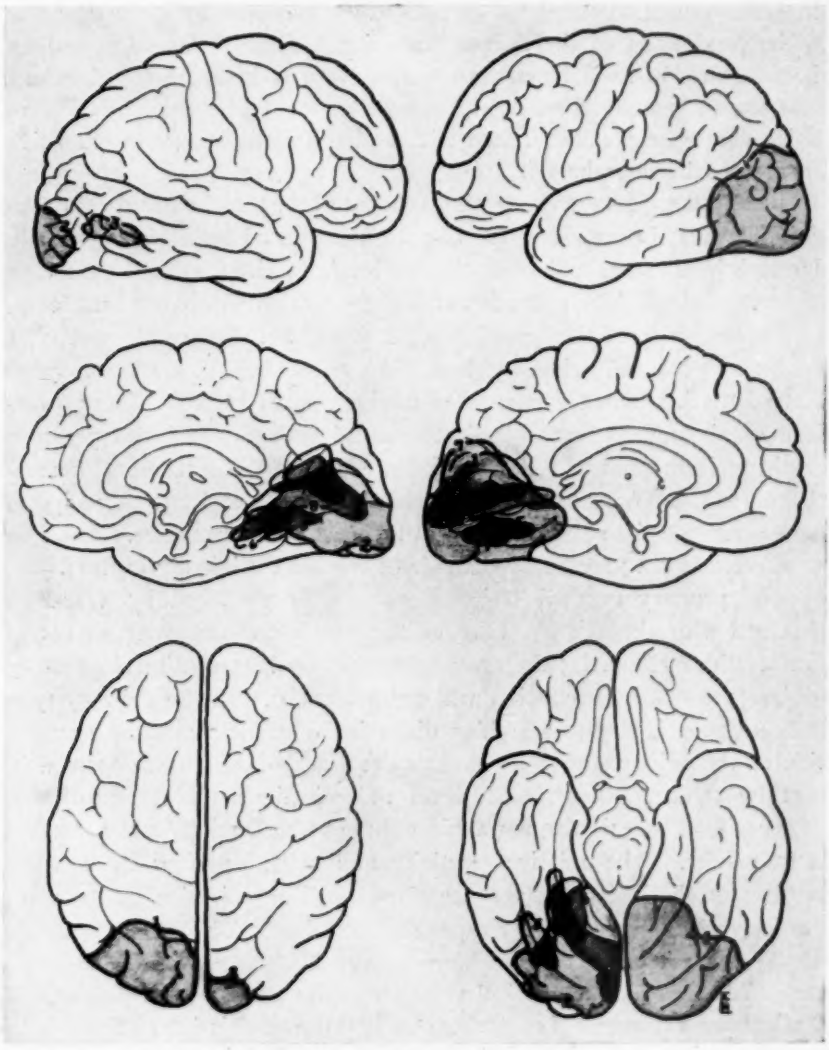

Fig. 3.—Drawings showing locations of diffuse contusions in cases 1 to 8. The numbers on the lines correspond to the case numbers.

practically the entire occipital lobe in another (fig. 3). This is true of both the primary and the secondary types. The involved region is not uniformly affected, the discoloration being most marked where the greatest degree of hemorrhagic infiltration occurs.

Only rarely are the overlying leptomeninges torn and then usually on the dorsolateral surface where the inner surface of the skull does not present a uniformly flat surface (case 1). Viewed externally the affected cortex at first assumes a mottled red appearance; after fixation it assumes a characteristic plum color. It resembles quite closely red softening secondary to thrombosis of the superficial cortical veins. The lesion is essentially a hemorrhagic softening, particularly of the cortex (fig. 4). The yellow softening of the subcortex is more likely due to

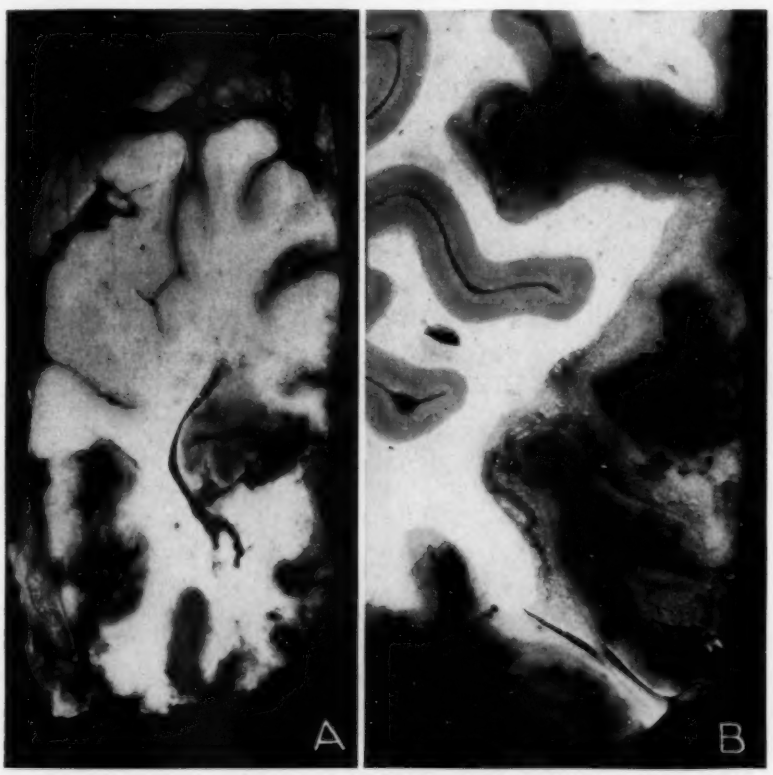

Fig. 4.—*A*, cortical hemorrhage and subcortical softening in case 1. *B*, diffuse and discrete cortical hemorrhages in case 2; enlarged ⅔.

impairment of the circulation resulting from the hemorrhagic infiltration of the cortex. The pressure of these accumulations of blood very likely interferes with the flow of arterial blood into the underlying white substance. The reddish coloration is due to the presence of myriads of small petechial hemorrhages, which may become confluent and thus not be clearly distinguishable from one another by the naked eye. In the subcortex the hemorrhages are often larger and more discrete.

The late appearance of this lesion is as yet unknown. Judging from the changes apparent after twelve days, one concludes that a more or less extensive atrophy and scarring of the cortex in the affected region will result. The scar will probably be a vascular one, as suggested by the tendency even in recent lesions to the formation of new blood vessels.

Histology.—In the first few days there is little to be seen except the disorganized cortex with the infiltration of red blood cells. One outstanding change and one which persists for days is the remarkable and widespread dilatation of the small blood vessels.

After several days have elapsed, evidences of cellular proliferation in the pia and arachnoid are observed with a resultant irregular thickening of these membranes. In the cortex the nerve cells begin to lose their coloration in routine stained preparations; specific methods show a loss of tigroid material and disintegration of the neurofibrils. Cells in the vicinity of the hemorrhagic areas show more serious evidence of injury than do those more remotely situated. The microglia show transitional forms. The endothelial cells of the blood vessels also show early evidence of proliferation.

After an interval of nine days (case 1) more advanced changes are observed. The pia-arachnoid has become a definitely thickened structure owing to the proliferation of spindle-shaped cells and to its infiltration with leukocytes. About some of the larger pial and cortical blood vessels may be found large collections of lymphocytes. Large numbers of leukocytes are found scattered throughout the cortex, presumably the result of the hemorrhage. The cortex shows an advanced disturbance of the normal cyto-architectonics incident to hemorrhage and softening. The nerve cells in the seriously affected areas appear largely as "ghost cells." Tigroid pigment is absent from their cytoplasm. The neurofibrils show extensive disintegration when stained by the reduced silver method of Cajal, some cells being entirely devoid of argentophilic material, others having local collections of small perinuclear granules. About the areas of hemorrhage both in the cortex and subcortex this method shows the nerve fibers to be intensely impregnated with silver (preservation necrosis of Cajal). End-bulbs may be disinguished at times in these areas where the nerve fibers have been interrupted.

All transitional forms of microglia are shown by the combined method. The areas of cortex undergoing softening are occupied with compound granular corpuscles loaded with blood pigment, free fat or granules of argentophilic material, depending on the preparation studied. Other forms of interstitial elements (oligodendroglia and neuroglia) are poorly demonstrated in these necrotic areas, many of them evidently undergoing necrobiotic change.

The smaller cortical blood vessels still show an intense congestion. In the margins of the necrotic areas are found groups of blood vessels which show active proliferation of their endothelium and the development of new vascular buds. With special methods the endothelial cells are found to contain fat and argentophilic granules.

In the underlying white substance routine stains show pale infarcted areas with altered nerve fibers crossing them. These are evidently the result of an impairment of circulation.

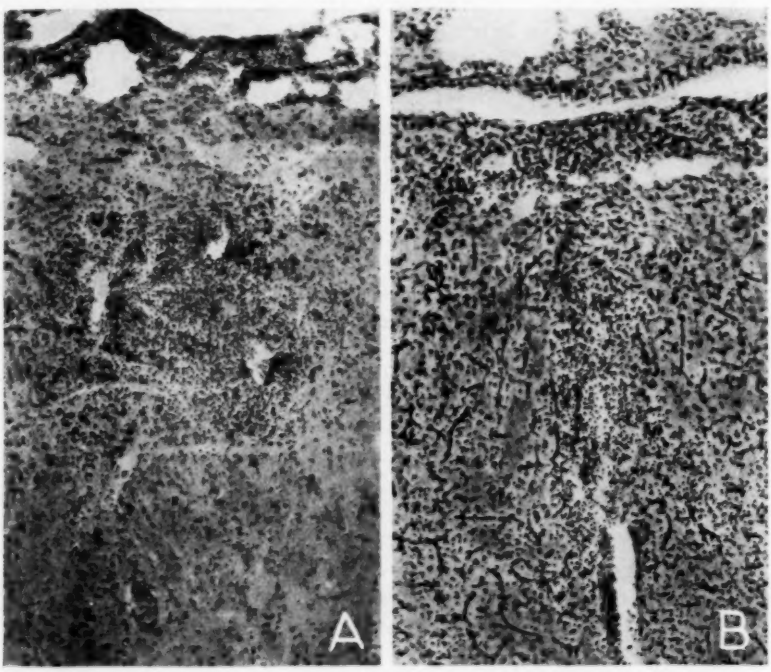

Fig. 5.—*A*, cortical and meningeal hemorrhage in case 1; hematoxylin and eosin; × 32. *B*, thickening of the pia mater and perivascular hemorrhage; combined method; × 32.

No opportunity has been offered to make a histologic study of the residual lesion after a period of months or years. One suspects that a vascular scar will result in the softened areas and permanent disorganization of the cortex as a result of the many areas of hemorrhage.

SUMMARY

Contusions of the occipital lobe are relatively uncommon. With the exception of those due to depressed fractures, they assume certain characteristics which are of interest in the study of traumatic intracranial

lesions. Diffuse contusion of the occipital lobe, characterized by a diffuse reddish coloration and softening of the affected cortex without gross morphologic disorganization, results from two types of mechanical disturbance: The lesion may be primary and acute, resulting from forcing of the occipital cortex against the falx or tentorium when the head in motion strikes some relatively immovable object. The force of the blow is expended on the sides or top of the head. Although in the primary type the contusion of the brain is usually found on the same side as that of the injury to the scalp, it occurs on the opposite side of the occipital lobe and is therefore a contrecoup. The secondary type is the result of local pressure by an expanding lesion such as edema or subdural or intracerebral hemorrhage. In this type there is no necessary relationship between the side of the original injury and that of the contusion. In any case the lesion is essentially a diffuse hemorrhagic softening of the cortex resulting from a rupture of small cortical veins incident to the sudden reversal of current in these vessels in the primary type, or to persistent and increasing obstruction by continued pressure in the secondary type. Microscopically, the cortical and subcortical tissues are found to be infiltrated with blood. The softening and disintegrating tissues are ultimately filled with compound granular corpuscles. The appearance of the ultimate lesion is unknown since no example has as yet been studied.

LIPIDS IN THE LIVER OF THE CAT DURING BILE STASIS AND BILIARY DECOMPRESSION

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AND

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There have been relatively few systematic studies of the effect of bile stasis on the quantity and distribution of lipids in the hepatic and Kupffer cells, and we have not found any reference to the effect of biliary decompression in this connection. In the course of studies of morphologic and functional changes occurring during experimental ligation of the common duct in cats, with subsequent release of obstruction, material was obtained suitable for a systematic study of this problem.

MATERIALS AND METHODS

Observations were made on thirty-nine cats during total bile stasis of from ten hours to forty-two days' duration and on twenty-one following biliary decompression of from one hour to seven days' duration. The animals were maintained on a diet of fresh scrap meat and milk. Comparative studies were made during stasis and decompression in the same animal in eleven instances. The animals were etherized, and the abdomen of each was clipped and washed with Harrington's solution, followed by alcohol. A midline incision was made, and the common duct was isolated. In some cases the duct was doubly ligated with linen thread and severed between the ligatures. In those animals which were to be subsequently subjected to decompression the duct was ligated close to the duodenum with linen tape 3 mm. wide tied in a double surgical knot. After varying periods of stasis the ligature was carefully removed. Only those animals are included in this report in which the contents of the ducts promptly filled the segment distal to the point of ligation. The animals were subsequently killed under light ether anesthesia at varying intervals following release of the obstruction. In a few cases death occurred spontaneously, and material from these animals was rejected if evidence of postmortem change was detected.

All cases were excluded in which the duct system was not perfectly patent and in which bile could not readily be expressed through the ampulla of Vater. In this way we have been able to time the duration of total stasis and of decompression with a reasonable degree of accuracy. In eleven cases biopsy specimens were obtained at the time of removal of the obstructing ligature for the purpose

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Aided by the Jefferson Medical College Hospital Tumor Clinic and the Martin Research Fund.

of comparing the lesions of stasis with those of decompression in the same animals. All animals are excluded from the present consideration in which complicating factors were found to exist; among these were (1) reconstruction of the common duct or the presence of accessory ducts during the period of supposed stasis, (2) infection, (3) spontaneous or traumatic rupture of the duct and (4) nonpatency of the duct system following removal of the ligature. In cats 63 and 84, which are included in this report, biliary decompression was accompanied by acute suppression of bile formation.

Specimens were fixed in diluted solution of formaldehyde, U. S. P. (1:10). Some were frozen, sectioned and mounted either unstained or stained with Nile blue sulphate, scarlet red, Fischler's [1] stain, dilute eosin and methylene blue; others were blocked in paraffin, cut and stained with hematoxylin and eosin and Mallory's and Van Gieson's connective tissue stains. Frozen sections (from 8 to 25 microns thick) were examined under crossed Nicol prisms for the presence of doubly refractile material.

EXPERIMENTAL OBSERVATIONS

Bile Stasis.—The findings in the thirty-nine animals in this group are presented in detail in table 1. The quantity of stainable lipid in both hepatic and Kupffer cells was extremely variable during the first seven days of stasis. It was absent from the hepatic cells in only two instances (147 and 119) and from the Kupffer cells in only one (146) during this period. With stasis of increasing duration the quantity of stainable lipid decreased rather abruptly and was practically absent in animals with stasis of from 15 to 42 days' duration.

There was likewise wide variation in the distribution of lipid in different portions of the lobules in different cases; this variation was apparently unrelated to the duration of stasis within the first seven days. Moreover, there was no consistent relationship between the quantity and distribution of stainable lipids in the hepatic cells and their quantity and distribution in the Kupffer cells during this period.

During stasis, after the first few days, this material, even when present in large amount, occurred in the form of small granules. In the normal cat stainable lipids, which are usually present in abundance, tend to occur as droplets or globules of larger size. With the Nile blue sulphate stain the greater part of the stainable material was blue; however, the subcapsular zone frequently contained pink or blue-pink granules, and occasionally variation in staining reaction was observed in different cells irrespective of their location.

In sections stained with hematoxylin and eosin vacuoles were noted which were not due to the presence of stainable lipid, as demonstrated by examination of frozen sections. In some cases they were found to be associated with doubly refractile, nonstainable material; in others they were due to the presence of glycogen, and in some instances their identity could not be demonstrated.

1. Mallory, F. B., and Wright, J. H.: Pathological Technique, ed. 8, Philadelphia, W. B. Saunders Company, 1924, p. 185.

Doubly refractile material was present in abundance in the Kupffer cells throughout all periods of stasis from ten hours to forty-two days. Except in a few cases of stasis of seven days' duration, much smaller quantities were noted in the hepatic cells. There was apparently no consistent relationship between the quantity and distribution of

TABLE 1.—*Results of a Study of the Effect of Bile Stasis on the Quantity and Distribution of Lipids in the Kupffer and Hepatic Cells*

Cat	Weight, Gm.	Days of Stasis	Stainable Lipid		Doubly Refractile Material	
			Kupffer Cells	Hepatic Cells	Kupffer Cells	Hepatic Cells
97	?	10 hrs.	+	++	++++	+
94	?	16 hrs.	++	+++	++++	++
69	?	20 hrs.	++	++++	++++	+
70	?	1	+	+	+++	±
144	1,340	2	+++	++	+++	+
143	3,700	2	++++	++	++++	++
147	3,800	2	++	0	+++	±
154	1,370	6	+	+	++	+
126	442	6	+++	±	++	±
119	3,090	6	+++	0	+++	±
146	1,630	6	0	+	++	+
145	2,610	6	+	+	++	+
151	740	7	+	+++	+++	+++
114	2,580	7	+	+++	+++	++
152	4,800	7	++++	+++	+++	+++
150	1,180	7	++	+++	+++	++
113	1,130	7	+	+	++	+
104	Kitten	7	+	++	+++	±
121	3,130	8	±	±	++	±
120	4,510	8	0	0	++	+
103	Adult	8	0	+	+++	±
28	Kitten	8	+	+	+++	±
102	Adult	8	0	0	+++	+
155	2,300	10	+	+	+++	++
123	3,160	10	±	±	++	±
101	Adult	10	+	+	++++	+
116	3,670	12	+	++	+++	+
25	Kitten	13	+	0	++	±
24	Kitten	15	0	0	+++	+
26	Kitten	15	0	0	+++	+
14	Adult	17	0	0	+++	+
50	Adult	18	+	+	++++	±
47	Kitten	20	±	±	++	0
58	Adult	22	0	0	++	±
60	Adult	25	0	0	++	±
51	Adult	27	0	0	++++	++
15	Adult	28	0	±	+++	±
54	Adult	30	0	0	+++	+
53	Adult	42	0	0	++	±

doubly refractile material and the quantity and distribution of stainable lipid. Frequently, the former was present in situations in which the latter was absent; on the other hand, at times the two were so intimately associated that the doubly refractile crystals produced marked irregularity in the outline of the stainable droplets and granules. In some instances these crystals occupied the central portions of the lipid droplets and granules, producing a vacuolated appearance in sections stained with Nile blue sulphate (fig. 1). Comparison of stained and unstained

frozen sections revealed an occasional discrepancy in the quantity of doubly refractile material. The reason for this is not apparent, since there was no consistency in this discrepancy. The tabulation of our observations is based on those sections showing the largest amount of this material in each case.

In stained and unstained frozen sections crystalline material was observed, the exact nature of which has not been determined. In Nile

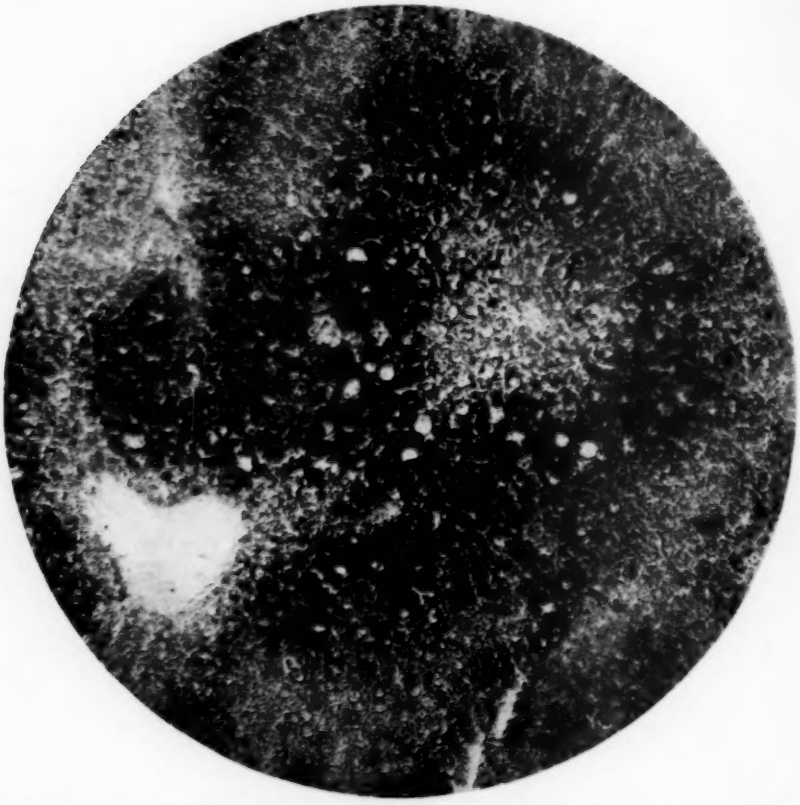

Fig. 1 (cat 94).—Stasis sixteen hours: Liver shows vacuoles in stained lipid droplets, due to the presence of doubly refractile material. Frozen section stained with Nile blue sulphate; about × 100.

blue sulphate preparations these appeared as needle-shaped or rod-shaped coarse crystals occurring singly or arranged in sheaves. They were noted as early as the sixteenth hour of stasis but were much more numerous and occurred more constantly in the later stages. These crystals were distributed irregularly throughout the lobule in patchy areas, being much more abundant in some lobules than in others. Within the lobule they appeared to be contained largely within Kupffer

cells, although the possibility that they were free within the sinusoids could not be definitely excluded. However, the fact that frequently large quantities of doubly refractile material in this situation extended to and stopped short at the central vein, none being present within the lumen of the latter, strongly suggests that these crystals were not free within the sinusoids. They were rarely observed in hepatic cells but were particularly numerous about and within the thickened portal radicles, in which situation they appeared in tissue crevices and within phagocytic cells. Similar crystals were seen in some cases lying free in the larger blood vessels where the serum had separated from the formed elements.

The great majority of these crystals were doubly refractile when examined under crossed Nicol prisms. In an attempt to establish their identity as fatty acids, Fischler's stain was applied, with inconclusive results. Many of the larger crystalline masses took the hematoxylin stain to some extent but also acquired a reddish cast; in some cases small, sharply defined black crystals could be seen in intimate association with those mentioned.

The stainable lipids, doubly refractile material and brownish crystals considered in the foregoing paragraphs bore no apparent relation to the degenerative and necrotic lesions occurring in the liver in the presence of bile stasis as described elsewhere.[1a] It is difficult to determine the presence or absence of any relationship between the quantity of stainable lipid and the sporadic degenerative and necrotic lesions during the first week of stasis; this is due chiefly to the coincidental abundance of lipids and the activity of degeneration and necrosis in the inner portion and sporadically throughout the lobule during this period. However, in the later stages extensive degenerative changes could be seen in cases in which stainable lipid was absent. Nevertheless, it is possible, of course, that the stainable lipid granules occasionally observed during the late period of stasis may be associated with the degenerative process in the hepatic cells.

The areas of focal necrosis present during the first thirteen days of stasis usually contained many small lipid granules within the shadowy outlines of necrotic and disintegrating hepatic cells which, together with the latter, were phagocytosed by macrophages. Lipid in this situation occurred independently of the presence or absence of stainable lipid in the remainder of the lobule. Doubly refractile crystals were rarely observed in areas of focal necrosis even when present elsewhere in the lobule.

1a. Stewart, H. L., and Lieber, M. M.: Arch. Path. **19**:34, 1935. Cantarow, A., and Stewart, H. L.: Am. J. Path. **11**:561, 1935.

The areas of hyaline necrosis beneath the capsule of the liver and about the portal radicles frequently contained droplets of stainable lipid occurring both within necrotic hepatic cells and within macrophages, which were apparently actively engaged in phagocytosing and removing the necrotic material. In the greatly thickened portal radicles resulting from the organization of hyaline necroses there were frequently collections of macrophages loaded with fat in immediate relation to the large bile ducts which were being destroyed. Stainable lipids were also present in the necrotic epithelial cells lining these ducts. We have not seen stainable lipid in the epithelial cells of the bile ducts during

TABLE 2.—*The Quantity and Distribution of Lipids in the Kupffer and Hepatic Cells Following Decompression*

Cat	Weight, Gm.	Days of Stasis	Days of Decompression	Stainable Lipid		Doubly Refractile Material	
				Kupffer Cells	Hepatic Cells	Kupffer Cells	Hepatic Cells
132	3,800	1	1	++++	+	++	±
131	3,230	1	1	+	+++	++	+++
147*	3,800	2	1	++	0	+++	±
143*	3,700	2	1	++++	+	++++	+
144*	1,340	2	1	+	++	+++	++
87	3,180	4	7	+	++	++	+
98	2,250	5	1	+	+++	+++	++
63	1,950	6	3	+++	+++	++++	+
86	2,400	7	1	+	+++	+++	+++
113*	1,130	7	4 hrs.	++	+++	+++	+
114*	2,580	7	1	++	+	+++	++
150*	1,180	7	1	±	+++	++	++
152*	4,800	7	3	+++	++	+	++++
120*	4,150	8	2 hrs.	+	+	+++	+
121*	3,130	8	1	±	±	+++	++
123*	3,160	10	1 hr.	±	±	++	±
122	4,280	11	1	+++	0	+++	+
64	1,950	11	1	+	+++	+++	+
116*	3,670	12	1	+	+	++	+
128	2,530	15	2	++++	±	++++	+
125	2,500	16	3	++++	±	++++	+

* Observed during stasis also (table 1).

stasis except when the ducts were undergoing destruction as a result of the organization of areas of hyaline necrosis.

Biliary Decompression.—The findings in the twenty-one animals in this group are presented in detail in table 2. The quantity of stainable lipid in both hepatic and Kupffer cells was extremely variable during all periods of decompression from one hour to seven days following total stasis of from one to sixteen days' duration. It was present in the Kupffer cells in every case and was absent from the hepatic cells in only two instances (decompression one day, stasis two and eleven days). The observations made during stasis regarding the variation in the distribution of stainable lipids and the absence of any consistent relationship between the quantity in the hepatic cells and that in the Kupffer cells were also true during decompression. Although occasion-

ally there seemed to be a distinct tendency toward droplet formation during decompression, in general the lipid material presented much the same appearance as during total stasis.

Comparative studies during stasis and decompression in eleven cases revealed nothing of particular significance except in cat 120, in which no stainable lipid was present in the hepatic parenchyma at the end of eight days of stasis whereas stainable lipid was observed in both hepatic and Kupffer cells two hours after release of the obstruc-

Fig. 2 (cat 128).—Stasis fifteen days, decompression two days: Liver shows large amounts of stainable lipid in Kupffer cells. Frozen section stained with Nile blue sulphate; about × 60.

tion. No change occurred in three animals, and a variable change was noted in the remainder, the nature of which may be observed by comparing the findings recorded in table 1 and table 2. Of particular interest is the fact that large amounts of stainable lipid were present in the Kupffer cells in cats 128 and 125 two and three days, respectively, after periods of bile stasis of fifteen and sixteen days' duration, at which time stainable lipid is almost invariably absent or present in only very small quantity (fig. 2). Doubly refractile material

was present in every case and differed in no essential respect from that observed during total stasis. Comparative studies in individual cases revealed relatively insignificant differences, which may be observed by referring to data presented in tables 1 and 2.

A peculiar lesion was noted in cat 132 twenty-four hours following relief of stasis of twenty-four hours' duration (figs. 3 and 4). Large

Fig. 3 (cat 132).—Stasis one day, decompression one day: Liver shows large sharply demarcated nodular lesion composed of vacuolated pigmented cells, apparently hepatic cells. Note two smaller nodules below and to the left of the large one. Hematoxylin and eosin; about × 450.

vacuolated deeply pigmented cells, apparently hepatic cells, were scattered throughout the liver and frequently were collected in groups of as many as thirty-five cells. The line of demarcation from the surrounding parenchyma was sharp and often consisted of a canaliculus. These lesions, which occurred indiscriminately in all parts of the lobule, were

regarded as probably localized areas of degeneration, the pigmentation being accentuated by the degenerated and vacuolated cytoplasmic background. These lesions contained large amounts of stainable lipid which stood out in sharp contrast to the hepatic cells in the remainder of the parenchyma, which were almost devoid of stainable fat. On the other hand, these areas contained few or no doubly refractile crystals although

Fig. 4 (cat 132).—Stasis one day, decompression one day: This shows the high lipid content of the nodular lesions illustrated in figure 3. Note the relative absence of stainable lipid in the hepatic cells and the large amount in the Kupffer cells. Frozen section stained with Nile blue sulphate; about × 200.

the Kupffer cells in the surrounding parenchyma contained relatively large quantities of such crystals.

COMMENT

The literature contains few studies of the effect of total bile stasis on the quantity and distribution of lipids in the liver, and no reference

could be found to studies of the effect of decompression in this connection. Mayer,[2] who is generally regarded as the first to study systematically the morphologic changes in the liver of the cat following ligation of the common duct, concluded from observations on four animals that fatty degeneration of the liver does not occur as a result of bile stasis. However, all of these animals showed peritonitis at autopsy. These findings were in direct contrast to those of Leyden[3] who, studying twenty dogs with total stasis of from one to thirty-three days' duration, reported an increase in hepatic fat during the period of stasis. All but one of these animals died of peritonitis. The work of Legg[4] is of distinct significance because of the relatively large number of animals employed (sixteen cats), the detailed report of the morphologic findings and the infrequency of gross infection despite the fact that aseptic technic was not employed. With the exception of one case in which large amounts of fat were present at the end of seven days of stasis, Legg found practically no fat droplets in the liver after the fourth day of stasis in the absence of spontaneous reconstruction of the common duct. His conclusions were as follows:

> As to the infiltration of the cells with oil, it is difficult to determine whether it is an accident or the result of the operation. The evidence would incline, I think, to the former. In those animals who lived into the second or third weeks, the large fat drops in the liver cells were no longer seen. They were replaced by granules, colorless and insoluble in acetic acid, probably therefore fat. This granular state of the cells may be looked upon as part of the atrophy caused by the growth of the connective tissue, just as in ordinary cirrhosis.

This problem has apparently never been subjected to systematic and detailed investigation, but the occasionally reported observations, usually incidental and sporadic, are summarized in the statement by Ogata[5] that with obstruction of the common duct hepatic fat is markedly reduced in almost all animals (guinea-pig, rat, rabbit, dog, mouse, frog, pigeon); these findings coincide with observations made on human beings. Ogata found fat in the hepatic cells during prolonged stasis in only one dog (thirty-five days) which was very obese.

Our findings in the present series are in accord with the earlier observations regarding the decrease in the stainable lipids of the liver in the later stages of stasis. It is interesting to note that although there was rather wide variation in the fat content of both hepatic and Kupffer cells during the first week of stasis a sudden marked decrease occurred at about the seventh day, even small quantities of stainable lipid being

2. Mayer, H.: Med. Jahrb., 1872, p. 133.

3. Leyden, E.: Beiträge zur Pathologie des Icterus, Berlin, A. Hirschwald, 1866, p. 83.

4. Legg, W.: St. Barth. Hosp. Rep. **9**:161, 1873.

5. Ogata, T.: Beitr. z. path. Anat. u. z. allg. Path. **55**:236, 1913.

seldom found after that time. There are few data available in the literature regarding the distribution of fat between the hepatic and Kupffer cells during total bile stasis. Although there was no consistent relationship between the quantities of stainable lipid in these two situations during the first week of stasis, the fact that it diminished simultaneously in both types of cells after that time is probably of significance.

The cause of the marked decrease in stainable lipid is not readily apparent. It is probably not dependent on impaired nutrition which, according to most investigators, is usually accompanied by an increase in hepatic fat. Furthermore, although these animals did not take a normal amount of food, they almost invariably ate some of the food offered them, and no relationship could be demonstrated between the state of nutrition and the fat content of the liver. The fact that in the first week of stasis there was no consistency between the distribution of fat and that of sporadic degenerative changes within the lobules, coupled with the fact that in the later stages fat was frequently absent from cells which were markedly degenerated, suggests that this variation in the amount of stainable lipid is not dependent directly on regressive changes in the cells. In the focal midzonal and hyaline necroses, however, the contained fat was at times obviously associated with the necrotic process, since the adjacent parenchyma was often free from fat. It is probable that the observed changes in the stainable lipids of the hepatic and Kupffer cells are dependent on some alteration in the metabolic activity of these cells incident to the state of total bile stasis. This hypothesis is perhaps supported by the fact that relatively large quantities of fat were present in animals (128, 125) two and three days after the relief of stasis of fifteen and sixteen days' duration; on the basis of our observations during total stasis, it is highly improbable that the hepatic and Kupffer cells contained even a small amount of stainable lipid at the time of the release of the obstructing ligature.

In view of the early studies of hepatic fat in bile stasis, which was almost invariably complicated by infection, the findings in certain of our cases in which suppurative cholangeitis was present at autopsy are of interest. These cases are not included in the material presented in the tables. A few animals with this condition were found to have rather large quantities of stainable lipid in the hepatic and Kupffer cells, particularly in the former, in the late stages of stasis, differing markedly in this respect from the animals in which the last stages of stasis were uncomplicated. A moderately large quantity of stainable lipid was observed in the Kupffer cells in one animal with stasis of twenty-nine days' duration; this animal, however, had been rendered acutely anemic by repeated withdrawal of large amounts of blood by cardiac puncture, which may have been responsible for the unusually large quantity of lipid present.

Double refraction of lipid material is indicative of the presence of large quantities of cholesterol and cholesterol esters in the lipid mixture. The apparent lack of quantitative relationship between the doubly refractile material and the stainable lipid in the Kupffer cells during total stasis suggests that the factors underlying the metabolism of these two classes of substances in the liver are essentially different. This difference was much more pronounced in the Kupffer than in the hepatic cells; in fact, in a few instances, particularly with stasis of seven days' duration, a relatively large quantity of stainable lipid in the hepatic cells was associated with a similarly large amount of doubly refractile material. This suggestive metabolic difference is further supported by the lack of consistent relationship in the distribution of stainable lipid and doubly refractile material in the hepatic cells.

Levine [6] found doubly refractile lipid substances consistently in the hepatic cells of twenty-seven human subjects who died of accidental causes, but was unable to demonstrate any in the Kupffer cells. On the basis of the observation of Anitschkow [7] and others that these cells store cholesterol and cholesterol esters removed from the blood stream, Levine stated that their absence in this situation under essentially normal conditions indicates that the cholesterol is probably passed to the hepatic cells too rapidly to be demonstrated in the Kupffer cells by the technic employed. However, we were able to demonstrate large quantities of doubly refractile lipid material in the Kupffer cells of normal animals studied in conjunction with the present experimental series. Nevertheless, the presence of consistently large amounts in the Kupffer cells and small amounts in the hepatic cells during total stasis suggests that the transfer of this material from the former to the latter is considerably impaired under these conditions and that some degree of impairment in this connection persists during decompression of one hour to seven days' duration.

SUMMARY

Studies were made of the quantity and distribution of stainable lipid and doubly refractile material in the liver in thirty-nine cats with uncomplicated total bile stasis of from ten hours to forty-two days' duration and in twenty-one cats following biliary decompression of from one hour to seven days' duration.

The quantity of stainable lipid decreased markedly in both hepatic and Kupffer cells during stasis and was practically absent in the majority of animals after the seventh day. A return of large quantities of stain-

6. Levine, V.: Arch. Path. **14**:345, 1932.

7. Anitschkow, N. N: Deutsche med. Wchnschr. **39**:741, 1913.

able lipid was noted in animals several days after relief from prolonged total stasis.

Doubly refractile material was present in the Kupffer cells in large quantities throughout the entire period of total stasis, differing markedly from the stainable lipid in this respect.

Although necrotic lesions frequently contained large quantities of fat, our observations during the early and late stages of stasis indicate that the stainable lipids distributed indiscriminately throughout the lobule are not necessarily dependent on regressive changes in the affected cells.

Stainable lipid was not observed in the epithelium of the bile ducts except in the later period of stasis at a time when the ducts were undergoing destruction as a result of organization of areas of hyaline necrosis.

It is suggested that the consistently large amount of doubly refractile material in the Kupffer cells and the relatively small quantity in the hepatic cells during stasis are dependent on a delay in the transfer of this material from the former to the latter under the experimental conditions.

RENAL DENERVATION

EFFECT OF DAILY INJECTIONS OF COLON BACILLI AND PITRESSIN ON THE DENERVATED KIDNEY OF THE DOG

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AND
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In previous experiments [1] on dogs in which unilateral denervation of the kidney had been performed one of us (G. M.) demonstrated by means of roentgenograms taken after injection of a suspension of bismuth oxychloride into the renal vascular bed that:

1. There is dilatation of the renal vascular bed after denervation.

2. The vascular bed of the denervated kidney does not contract after the intra-arterial injection of epinephrine, indicating the completeness of the denervation.

3. The denervated kidney is not damaged by repeated chilling, as is the normal kidney.

4. A single injection of a toxic agent, such as snake venom, causes greater changes in the denervated than in the normal kidney.

Of that series of twenty-six dogs killed from one to six months after renal denervation, the majority displayed an increase in the size of the denervated kidney; in a few the denervated kidney was slightly smaller, and in one the organ on which operation was performed was definitely contracted.

On the basis of these observations further experiments were undertaken to determine the response of the denervated kidney when exposed to various agents over long periods. Unilateral renal denervation through the lumbar route was carried out in a group of dogs, and a period of approximately two weeks was allowed for complete recovery. The dogs were divided into three groups. Each animal of the first group received 1 cc. of a two day broth culture of colon bacilli intravenously daily. No immediate effects were noted from the injections. The second group received 1 cc. of pitressin intravenously daily. In most instances the injection was followed in a few minutes by vomiting and defecation, and even with this dose some animals died. The

From the Department of Pathology and Bacteriology, University of Illinois College of Medicine.

1. Milles, G.; Müller, E. G., and Petersen, W. F.: Arch. Path. **13**:233, 1932.

third group received 1 cc. each of the broth culture of colon bacilli and of pitressin intravenously. The immediate reaction of these animals to the injection were the same as those of the second group. The injections were made daily—those of pitressin with the idea of producing repeated vasoconstriction and those of the colon bacillus as a bacterial agent of rather low virulence capable of doing damage to tissues.

After from three to eight weeks the animals were killed and the kidneys weighed. Tissues were fixed in formaldehyde and stained with hematoxylin and eosin and with azocarmine and methylene blue [2] for microscopic study. Ten dogs of the series survived long enough to be of value in this report.

EXPERIMENTAL INVESTIGATION

Group 1.—Daily intravenous injections of colon bacilli were made.

Dog 1.—Denervation of the left kidney was performed on Feb. 21, 1934, and the dog died on March 8.

The normal kidney weighed 40 Gm. Its capsule stripped readily, leaving a smooth, brownish-red surface. On the cut surface the cortex was of average width, grayish red and sharply demarcated from the medulla.

Microscopically the glomeruli were normal. The tubular epithelium was well preserved. The blood vessels were moderately dilated and contained a considerable number of pigment-filled macrophages. In a single area the normal structures had been replaced by dense hyalinized connective tissue, blending with a focus of round cell infiltration.

The denervated kidney weighed 25 Gm. Its capsule was thickened and gray and stripped with considerable resistance. The surface was pale gray to grayish pink. The cut surface was pale gray; the cortex was narrowed, and the medulla was poorly demarcated.

Microscopically the glomeruli were distended. Bowman's space was free from contents, and Bowman's capsule, which was composed of the usual flat cells, was in many instances surrounded by a zone of round cell infiltration, which usually extended into the interstitial tissue along the blood vessels. Moderate degenerative changes, chiefly in the form of cloudy swelling and occasional necrosis, were present in the tubular epithelium. There was moderate increase in the interstitial connective tissue. The blood vessels were markedly dilated and densely packed with red cells and pigment-filled macrophages. The smaller arterioles displayed moderate increase in the thickness of their walls and of the perivascular connective tissue.

Dog 2.—The kidney was denervated on February 21, and the dog was killed on June 19.

The normal kidney weighed 40 Gm. It was normal in gross appearance, answering to the same description as that of the corresponding kidney of dog 1.

Microscopically the glomeruli were of moderate size; there was an increase in the number of their cellular elements, particularly of the interstitial cells. Bowman's space was free from contents; Bowman's capsule was composed of a single layer of flat cells. In an occasional glomerulus the basement membrane

2. McGregor, L.: Am. J. Path. **6**:347, 1930.

of Bowman's capsule was proliferated and hyalinized. In such instances the afferent vessel was thick-walled; its lumen was narrowed, and a more or less well defined mantle of round cells was seen about the glomerulus. The tubular epithelial cells were fairly well preserved, although rather small, and a considerable amount of granular débris was present in their lumens. The arterioles were moderately thick-walled, and many of them were surrounded by a mantle of round cells.

The denervated kidney weighed 40 Gm. The capsule was thickened; otherwise the kidney showed no marked gross difference from that on which no operation was performed.

Microscopically the glomeruli were larger and the capillaries more dilated, and varying degrees of interstitial hyalinization were present; otherwise the section was essentially the same as that taken from the kidney on which no operation was performed.

Dog 3.—Denervation was performed on March 23, and the dog was killed on June 19.

The normal kidney weighed 35 Gm. The capsule was thin and stripped readily, leaving a smooth, dark brownish-red to purplish-red surface. On the cut surface the cortex was well preserved and dark brownish red and the markings were sharply defined. The medulla was clearly demarcated.

Microscopically the glomeruli were rather variable in size and appearance; some were large and cellular, and others were inconspicuous with small pyknotic nuclei and markedly increased and hyalinized interstitial tissue. In others there was loss of capillary tufts so that in some instances only a single atrophic tuft remained. Bowman's space contained a variable amount of homogeneous, pale-staining material, and Bowman's capsule varied from a single flat to a single swollen layer of cells, or to several layers of cells. The tubular epithelium was narrowed; the lumens of the tubules contained a considerable amount of granular débris. Here and there, an arteriole with a markedly thickened and hyalinized media and marked proliferation of perivascular connective tissue was seen. In such vessels the lumen was small. Except for the moderate degree of perivascular fibrosis there was no increase in the connective tissue.

The denervated kidney weighed 20 Gm. Its capsule was thick, gray and adherent. The surface was pale gray, and the consistency was markedly denser. On the cut surface the cortex was pale and narrow, and the medulla was poorly demarcated.

Microscopically (fig. 1) the following picture was uniformly present: The glomerular tufts were small, cellular and generally fairly well preserved. Bowman's space was free from contents. There was moderate to marked proliferation of the basement membrane of Bowman's capsule. Around many glomeruli a narrow mantle of round cells was seen. The tubules showed marked degenerative changes: their cells were flat or entirely lost, and their lumens were filled with hyaline plugs. There was marked increase in the interstitial connective tissue, which replaced the tubules to a large extent. The arterioles were thick-walled and hyalinized, and vacuolation of the intimal and medial cells was present. The arterioles were surrounded by a mantle of proliferating connective tissue.

Dog 4.—The kidney was denervated on April 26, and the dog was killed on June 21.

The normal kidney weighed 55 Gm. Grossly it appeared normal.

Microscopically an occasional glomerular tuft presented degeneration of a single loop, and in a few Bowman's spaces granular débris and red blood cells

were seen. The tubular epithelium was well preserved. The blood vessels were moderately distended with red cells.

The denervated kidney weighed 40 Gm. The capsule was thick, pale gray and markedly adherent. The renal parenchyma was pale gray to grayish pink.

Microscopically the glomerular tufts were compact and displayed rather marked cellular proliferation. Bowman's space was free from contents, and Bowman's capsule in many instances was thickened as a result of the proliferation of the

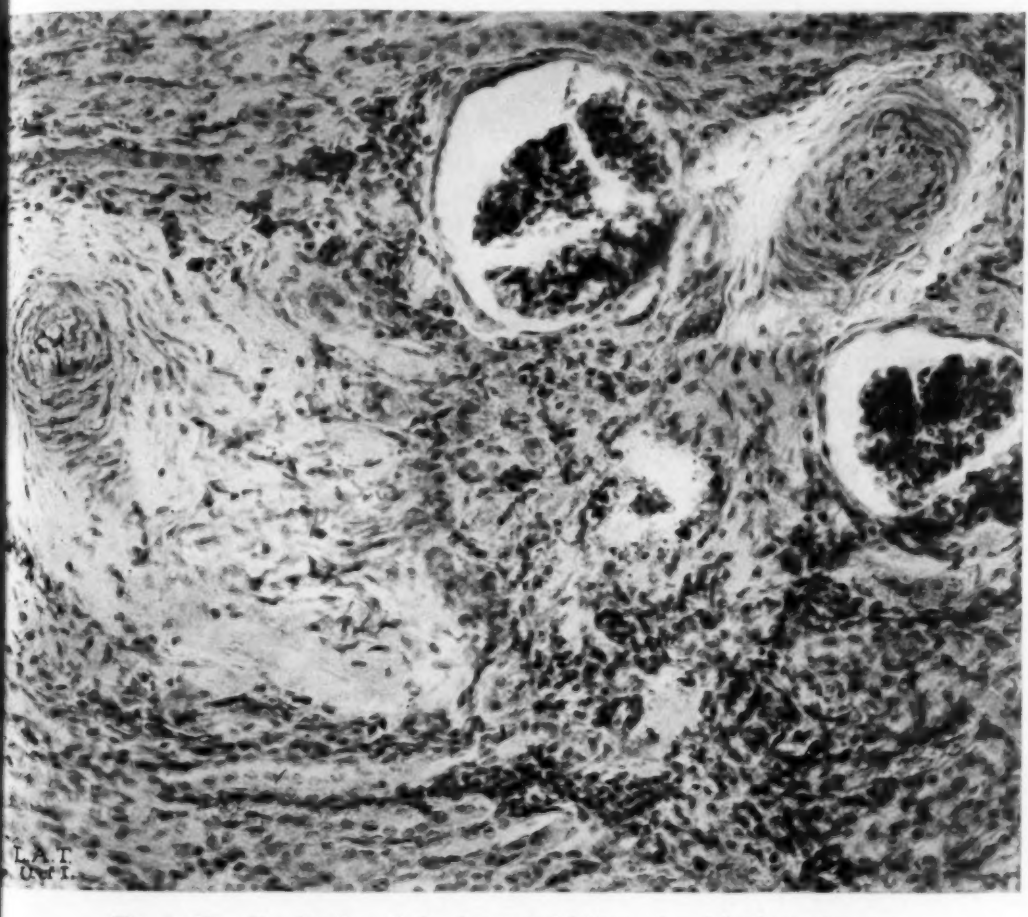

Fig. 1 (dog 3).—Section of the denervated kidney after injections of a suspension of B. coli daily for three months. Hematoxylin and eosin stain; × 240.

basement membrane. There was marked focal proliferation of the interstitial connective tissue, which radiated from the thick-walled arterioles. The lumen of the arterioles was diminished. The tubular epithelium was narrow and atrophic, and in the areas in which proliferation of interstitial connective tissue was most marked the tubules were entirely replaced. This section showed marked focal increase of connective tissue, which was especially well brought out by the azocarmine stain.

Dog 5.—The operation was performed on May 1, and the dog was killed on June 21.

The normal kidney weighed 33 Gm. Grossly the kidney appeared normal.

Microscopically the glomeruli were compact and cellular, and their capillary tufts were moderately dilated. The tubular epithelium was fairly well preserved. The blood vessels were normal in appearance, and there was no increase of interstitial connective tissue.

The denervated kidney weighed 37 Gm. The glomerular tufts were more markedly dilated and variable in their cellular content than those of the normal kidney. The tubular epithelium was well preserved. The blood vessels displayed no pronounced change except that they were moderately distended with red cells.

Summary of Group 1.—The daily intravenous injection of a suspension of colon bacilli into the five dogs of this series in which unilateral renal denervation had been performed resulted, after a period of two months, in demonstrable proliferation of the media of the small arterioles and proliferation of the adventitial connective tissue of the vascular coat. There was an associated low grade inflammatory reaction with interstitial fibrosis and scarring, involving almost exclusively the denervated kidney in four of the animals. The denervated kidney was markedly decreased in size in three animals, increased in one and unchanged in the fifth.

Group 2.—Daily intravenous injections of pitressin were given.

Dog 6.—The animal appeared normal on April 3 and was killed on July 25.

The kidney on which operation had been performed weighed 40 Gm. and appeared normal on gross examination.

Microscopically the glomerular tufts were large, and their capillaries were distended so that Bowman's space was present as a narrow slit in most instances. In an occasional glomerulus necrosis of a single loop was seen to have occurred, and red cells were present in Bowman's space. In other instances the glomerulus was smaller than its neighbors, and Bowman's capsule was thickened and hyalinized. The basement membrane of these glomeruli was proliferated and surrounded by a mantle of round cells. Adhesions between the capsule and the tufts were seen in a few instances. These changes were focal in their distribution. The arterioles were moderately thick-walled, and there was increase in the perivascular and interstitial connective tissue. The tubular epithelium was well preserved, although the cells were somewhat smaller than normal, and a small amount of débris and a few hyaline plugs were seen in the lumen.

The denervated kidney weighed 22 Gm. The capsule was thick, pale gray and adherent. The cortex was narrow, very pale pinkish gray and poorly demarcated from the medulla.

Microscopically (figs. 2 and 3) the tissue was the seat of profound changes characterized by diminution in the size of the various structures so that the glomeruli were arranged close together. The glomerular tufts displayed more or less marked atrophic changes, and in practically all the instances there was marked proliferation with more or less hyalinization of the basement membrane of Bowman's capsule. The tubules were almost entirely lost, having been replaced by markedly proliferated interstitial connective tissue. Their small lumens, particularly those of the collecting tubules, contained hyaline plugs. The arterioles

were markedly thickened; their lumens were markedly narrowed or completely obliterated, and there was marked proliferation of perivascular connective tissue as well as of the interstitial connective tissue already described, which was the seat of diffuse round cell infiltration.

Dog 7.—Denervation was performed on May 1, and the dog was killed on June 9.

The normal kidney weighed 38 Gm. Grossly it appeared normal.

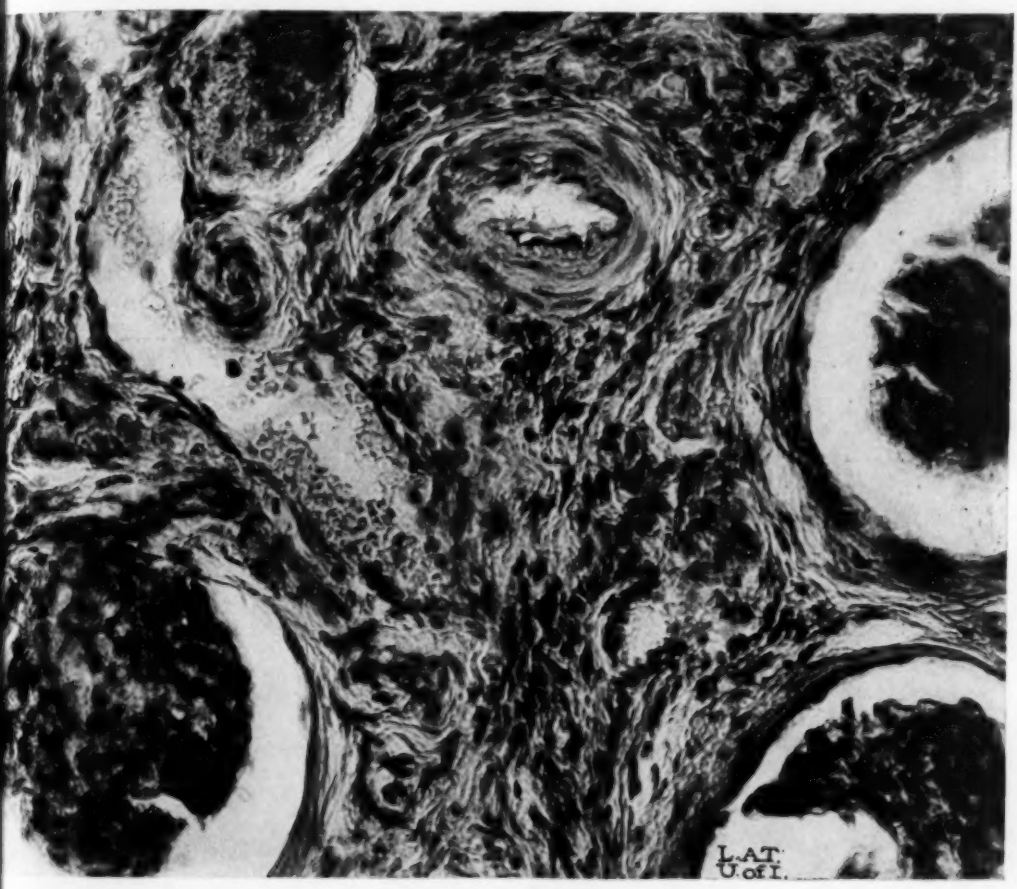

Fig. 2 (dog 6).—Section of the denervated kidney after intravenous injections of 1 cc. of pitressin daily for three months. Hematoxylin and eosin stain; × 480.

Microscopically the glomeruli were distended; the capillaries were filled with red cells, and Bowman's space was free from contents. Bowman's capsule was composed of a single layer of flat cells. The tubular epithelial cells were granular, and their free margins were frayed. There was a moderate degree of cellular desquamation into the lumens. The larger blood vessels were distended with red cells.

The denervated kidney weighed 38 Gm. The capsule was slightly thickened and moderately adherent.

Microscopically the glomeruli were essentially normal. The tubular epithelium was well preserved. The larger vessels were widely distended with red cells. There was no increase in perivascular or interstitial connective tissue in either section.

Dog 8.—Unilateral nephrectomy was performed on April 26, and the dog was killed on May 31.

The kidney weighed 25 Gm. Grossly it appeared normal.

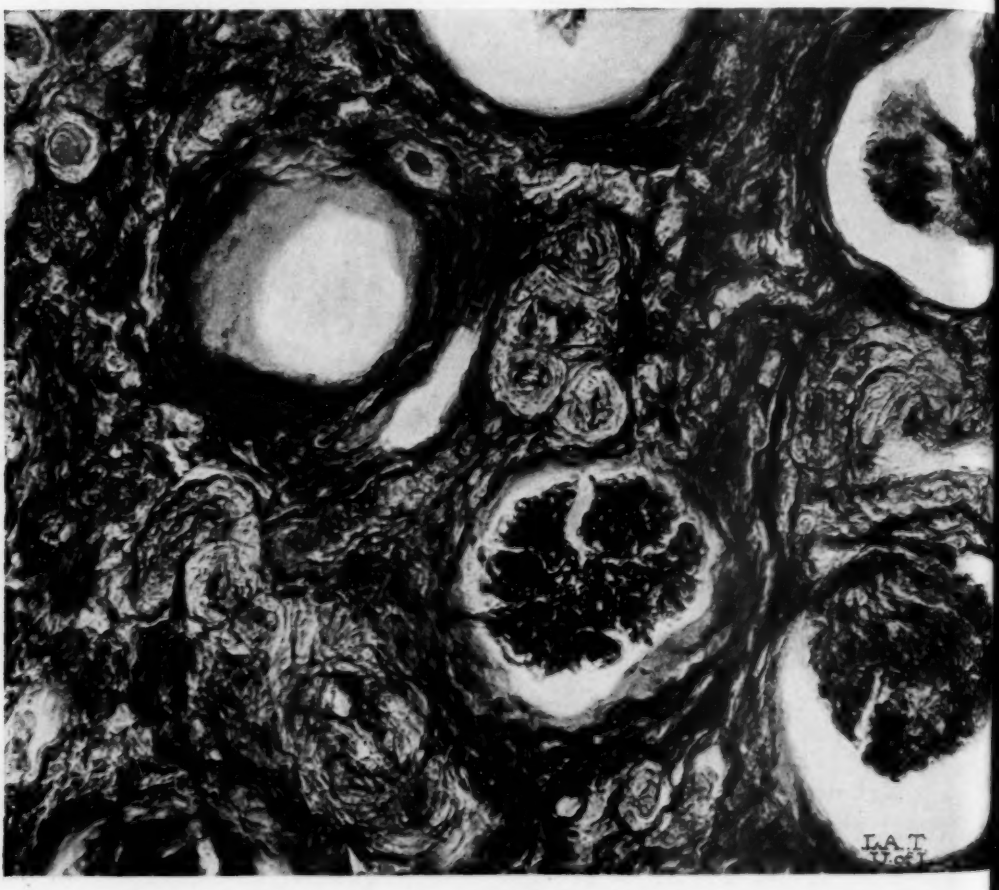

Fig. 3 (dog 6).—Section of the denervated kidney after intravenous injections of 1 cc. of pitressin daily for three months. Azocarmine and methylene blue; × 400.

Microscopically the kidney showed moderate hyaline changes in the glomerular tufts, granular débris filling Bowman's spaces, marked edema and proliferation of the interstitial tissue widely separating the tubules. There were profound degenerative changes in the tubular epithelial elements. These epithelial cells were present as an amorphous or granular mass in which only a few nuclear shadows remained and the cellular boundaries were entirely lost. The smaller

arterioles were diminished in size; the intima was moderately proliferated; the media was hyperplastic, and there appeared rather marked proliferation of the perivascular connective tissue.

Summary of Group 2.—Because of deaths after the injection of doses of pitressin larger than 1 cc. and occasional deaths even with a dose of 1 cc. of pitressin intravenously, only three dogs survived long enough for the experimental data to be used in this report. In the kidney of one dog pronounced perivascular and interstitial fibrosis, associated with marked round cell infiltration, similar to that seen in some of the dogs receiving colon bacilli, occurred. In the other dog the denervated kidney appeared to withstand the injections of pitressin with less resulting damage than did the kidney on which no operation was performed. In the unilaterally nephrectomized animal the remaining kidney was uninjured by a month of treatment.

Group 3.—One cubic centimeter of pitressin and 1 cc. of a suspension of colon bacilli were given daily.

Dog 9.—Denervation was performed on June 27, and the animal was killed on September 5.

The normal kidney weighed 21 Gm. The capsule stripped readily. The surface was smooth and dark brownish red.

Microscopically the glomeruli were large, more or less completely filling Bowman's space. In focal areas radiating through the cortex from the surface toward the medulla were zones in which the interstitial connective tissue was proliferated and infiltrated with round cells. There was rather pronounced round cell infiltration of the periglomerular interstitial tissue. In these areas the tubular epithelium was narrow and atrophic. In the intervening areas the tubules were well preserved. The blood vessels in the zones of fibrosis were moderately to markedly thick-walled and were surrounded by a dense zone of proliferated connective tissue.

The denervated kidney weighed 21 Gm. It presented essentially the same appearance as that of the kidney on which no operation was performed, except that the zones of fibrosis were neither as numerous nor as marked.

Dog 10.—The left kidney was denervated on June 27, and the dog was killed on September 5.

The normal kidney weighed 35 Gm. and grossly appeared normal.

Microscopically the glomeruli were well preserved; the tubular epithelium was moderately narrowed, and the free margins of the cells were frayed. A moderate amount of granular débris was present in the tubular lumens. In a few foci there was proliferation associated with round cell infiltration of the interstitial connective tissue.

The denervated kidney weighed 27 Gm. The capsule was thickened and adherent.

Microscopically the glomeruli were large; there was moderate atrophy of the loops, and the capillaries were distended with red cells. Bowman's space was free from contents, and the basement membrane of Bowman's capsule was moderately proliferated. There were scattered round cell infiltration of the interstitial tissue and marked atrophy of the tubular epithelium. The arterioles were thick-walled and hyalinized, and their lumens were markedly diminished in caliber.

Summary of Group 3.—In one of the two dogs which survived the combined injections of colon bacilli and pitressin, the denervated kidney showed approximately the same changes as those of the normal kidney, whereas in the second dog marked fibrosis with interstitial inflammation was noted.

COMMENT

In one animal of the earlier series of twenty-six dogs on which one of us reported [1] spontaneous diffuse atrophy and fibrosis of the denervated kidney were noted. In the present series of dogs which received injections of colon bacilli or of pitressin, or of both bacilli and pitressin, marked fibrosis associated with chronic inflammation in the denervated kidney developed in more than one half of the animals surviving for a month. These changes involved the interstitial tissue, the basement membrane of Bowman's capsule and, more markedly, the arterioles. The chronic, low grade inflammation, whether ascending or hematogenous in origin, was aggravated by the vascular changes resulting from denervation. Such pathologic changes are seen to a slight degree in old dogs, but never to the degree observed in these experiments. It is apparent that denervation in itself predisposes to the pathologic changes described and that the changes are hastened by a variety of agents which are capable of causing mild arteriolar injury.

The results can best be interpreted in the light of the function of the renal nerves and of the experimental results that have been obtained after denervation.

Although experimental work has been reported supporting the theory of a secretory function, the mass of evidence favors vasomotor and sensory control as a dominant, if not the only, function of the renal nerves.[3] The removal or destruction of the nervous pathway gives rise to functional changes which can directly or indirectly be ascribed to the loss of this vascular control. Chief among these immediate changes are increase in the volume and diminution in the specific gravity, but there is increase in the amount of the total solids of the urine. Apparently the secretory pressure of the urine remains unchanged.[4]

Rhoads and his associates [5] were unable to demonstrate a consistent change in renal blood flow or urea clearance after denervation or

3. Gironcoli, F.: Ztschr. f. urol. Chir. **27**:266, 1929. Hesse, E.: Surgery of the Vegetative Nervous System, Moscow, Staatsverlag, 1930, p. 243. Kuntz, A.: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929, p. 271. Ellinger, P. A., and Hirt, A.: Arch. f. exper. Path. u. Pharmakol. **106**:135, 1925.

4. Bieter, R. N.: Proc. Soc. Exper. Biol. & Med. **26**:792, 1929.

5. Rhoads, C. P.; Van Slyke, D. D.; Hiller, A., and Alving, A. S.: Am. J. Physiol. **110**:392, 1934.

cocainization of the renal pedicle of the transplanted kidney in dogs from which the opposite kidney had been removed. Their experimental methods were not entirely comparable to those of the other workers in the field. Their work indicates a marked automaticity of the renal vascular bed, which resulted in its control in the absence of the normal nerve supply and which probably accounts, to some extent at least, for the inconsistency in our results. This conclusion is supported by the fact that the vascular response of the denervated ear of the rabbit to experimental fever is similarly inconsistent (Pinkston [6]).

The denervated kidney presents a definitely altered response to toxic agents, such as corrosive mercuric chloride, uranium acetate, cantharides and snake venom, in that it appears to be more susceptible to damage than does the normal kidney. This may be explained by the inability of the denervated kidney to protect itself against toxic agents through vasoconstriction.

Of special importance are the reactions of the normal and the denervated kidney to bacteria which may be present in the blood stream. Hecht,[7] using rabbits, demonstrated that bacterial emboli are fewer and abscesses less numerous in the denervated than in the normal kidney after a single intravenous injection of a suspension of staphylococci. Müller and his associates [8] reported that with a continuous intravenous injection of a suspension of colon bacilli, after from forty to sixty minutes when chilling occurred, the bacteria as well as blood and albumin were excreted in the urine from the normal kidney. The blood cells and albumin give evidence of renal injury. The denervated kidney continued to excrete sterile and clear urine. He presumed that vasoconstriction occurring with the chill lowered the resistance of the renal tissue to the point at which the kidney was unable to withstand the injurious effects of the bacteria. In order to test this hypothesis further he first chilled the animals by means of an ice pack and then began continuous intravenous injections of colon bacilli. He reported that, instead of an interval of from forty to sixty minutes before changes were noted, bacteria, blood and albumin were found almost immediately in the urine from the normal kidney, whereas the denervated kidney continued to excrete urine which was apparently unchanged. One of us [9] studied the urine collected separately from normal and denervated kidneys and observed certain phenomena in connection with the intravenous injection of bacteria. After a single intravenous injection of

6. Pinkston, J. O.: Am. J. Physiol. **110**:448, 1934.

7. Hecht, R.: Proc. Soc. Exper. Biol. & Med. **29**:212, 1931.

8. Müller, E. F.; Petersen, W. F., and Rieder, W.: Verhandl. d. deutsch. Gesellsch. f. inn. Med. **42**:580, 1930.

9. Milles, G., and Nedzel, A. J.: Proc. Soc. Exper. Biol. & Med. **29**:976, 1932.

a suspension of Bacillus prodigiosus the urine from the normal kidney contained the organisms in far greater numbers than did that from the denervated kidney. Previous injury with snake venom decreases the ability of the normal kidney to excrete bacteria but does not alter the relative rates of bacterial excretion of the normal and denervated organs.

The work of Dastre and Morat,[10] amply corroborated and extended by Petersen and Müller,[11] demonstrated a balance of vasomotor tonus between the peripheral, or better the extraperitoneal, and the intraperitoneal splanchnic vascular bed. Briefly, this consists in the two divisions of the vascular bed of the organism being in opposite states of vascular tonus. In this grouping the kidneys are oriented with the skin. In experiments with acute injury it is apparent that the vasomotor nerves of the kidney cause constriction in the renal vascular bed during a chill, concomitant with vasoconstriction in the skin. With the vasoconstriction in the kidney the mechanical effect of washing with a large volume of blood which normally interferes with the localization of bacteria (stoppage) is lost. More important, however, is the diminution of the blood supply to actively metabolizing tissues, with the resultant local anoxemia and failure of removal of tissue metabolites. These factors lower the local resistance of the tissues and markedly increase the tendency of bacteria to localize. The normal fluctuations in the renal vascular bed which produce areas of vasoconstriction and vasodilatation have a similar, but much less marked effect. Exposure and chilling, such as are a common experience of persons in the rigorous climates, have perhaps even more effect in causing the localization of bacteria in the kidneys. Thus, a common history of onset in acute nephritis is one in which the complaint began with exposure and chilling, which, as we have experimental evidence to prove, produce marked peripheral and renal vasoconstriction. Conversely, with the surgical removal of the renal nerve supply a more or less permanent vasodilatation occurs, which is unaffected by the nervous orientation of the rest of the organism. In experiments dealing with acute infection it prevents the excretion of bacteria into the urine and defeats the localization of bacteria, with the resultant injury to the tissue of the kidney by the organisms.

Destruction of the renal nerve supply appears to have an entirely different effect if the animal is subject to repeated insults, judging from the experiments which we have already detailed. In analyzing these results the fact that the denervated kidney is likely to be damaged

10. Dastre, A., and Morat, J. P.: Recherches expérimentales sur le système nerveux vaso-moteur, Paris, G. Masson, 1884.

11. Petersen, W. F., and Müller, E. F.: Arch. Int. Med. **40**:575, 1927.

severely by daily intravenous injection of pitressin or colon bacilli, or both, is apparent. In order to explain this one must conclude that when deprived of the normal nerve supply the renal vascular bed goes into a state of atonic dilatation and that this results, after a period of time, not in improved but in reduced renal circulation as the result of stasis. Under these circumstances the denervated kidney would be protected against the spastic effects of a single injection of a noxious agent. When, however, the insult is repeated daily for a period of time direct injury to the tissues occurs, as is indicated by a low grade, proliferative inflammation, the result of the summation effects of the circulatory disturbance and the noxious agent. Theoretically, the same effects might be observed after denervation even without the injection of an injurious agent, since the degree of dilatation and stasis obtained must vary in different animals. This was noted but once in a series of twenty-six dogs.[1] Physiologically, renal function is usually unimpaired for as long as two months after bilateral denervation without the injection of a noxious agent (Caldwell, Marx and Rowntree[12]). Nisio[13] and Seres[14] observed degenerative changes in the kidney after denervation in some animals. The kidneys, which are observed to be the site of the marked degenerative changes described, are pale on gross examination, owing to anemia which is the result of the marked vascular fibrosis seen histologically.

In short, after denervation the renal vascular bed undergoes a period of dilatation and improved circulation lasting but a few weeks or months. This gives way to a period of dilatation and stasis. The resulting stasis and anoxemia plus an additional noxious factor, or occasionally the first condition without the second agent, gives rise to a low grade interstitial inflammation with marked proliferation of connective tissue.

Much the same condition may be visualized as occurring even in the normal kidney. As the result of the summation of the normal wavelike fluctuations in the vascular tone fortified by marked fluctuations in the environmental factors, especially the meteorological,[15] the kidney may be in a state of dilatation and stasis, equivalent to denervation, for variable periods. Under these circumstances, transient bacteremia or toxemia, encountering the kidney in a state of minimal resistance, would inflict damage mounting with each recurrence.

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12. Caldwell, J. M.; Marx, H., and Rowntree, L. G.: J. Urol. **25**:351, 1931.

13. Nisio, cited by Gironcoli.[3]

14. Seres, M.: Rev. méd. de Barcelona **1**:220, 1924; abstr., Ztschr. f. urol. Chir. **17**:54, 1925.

15. Petersen, W. F., and Milliken, Margaret E.: The Patient and the Weather: vol. III. Mental and Nervous Diseases. Vol. II. Autonomic Dysintegration, Ann Arbor, Mich., Edwards Brothers, Inc., 1934.

SUMMARY

After denervation the dog's kidney was observed to be subject to mild chronic inflammatory and marked degenerative changes when it was subjected to repeated injections of colon bacilli or pitressin, or of both. We conclude that this is the direct result of the loss of nervous control with attendant dilatation and stasis lowering the resistance of the tissue to the injurious agents to which the organism was subjected repeatedly for long periods of time.

MECHANISM OF ACUTE INFLAMMATION

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This discussion will be limited to the early vascular and cellular phenomena which develop in and about an area of local injury to the tissue. This response to an injury consists essentially in changes in the caliber and permeability of vessels, the development of an exudate locally and leukocytosis both general and local. The subsequent phases of local inflammation will not be discussed. A group of observations furnished by various workers may be assembled and correlated into an intelligible picture of the mechanism of inflammation.

Ebbecke's [1] physiologic studies on vascular reactions to irritation suggested a new interpretation of such reactions. His results illustrated Pflüger's dictum that physiologically the conditions giving rise to a need likewise provide for supplying it (Die Ursache des Bedürfnisses zugleich die Ursache für die Befriedigung des Bedürfnisses). He showed that irritational and inflammatory hyperemia result not from nerve stimuli but from substances released locally by tissue cells and that following mechanical, electrical or chemical stimulation such substances affect the adjacent vascular structures, causing dilatation, slowing of the blood flow, increased permeability of the capillaries and edema. This capillary-dilating substance was similar in its action to Heidenhain's lymphagogues and to the substances which produce urticaria, foreign protein reactions and the like. Ebbecke explained the cellular proliferation seen in later stages of inflammation as being due to a "wound hormone" derived from the injured tissue. This interpretation is supported by the recent demonstration of growth-stimulating substances such as trephones both in vivo and in vitro.

The mechanism of local vascular reactions in human skin was studied extensively by Lewis [2] and his associates. Mechanical or other forms of irritation are followed by a reaction with uniform characteristics regardless of the type of irritation. This reaction consists in (1) local dilatation and hyperemia of the minute vessels, (2) a spreading flare resulting from reflex dilatation of adjacent arterioles and (3) a pale circumscribed wheal resulting from increased permeability of the walls

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1. Ebbecke, U.: Arch. f. d. ges. Physiol. **169**:1, 1917; **199**:197, 1923.

2. Lewis, Thomas: Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

of the capillaries. Chemical examination of the fluid from such wheals revealed it to have a protein content closely approximating that of blood plasma. It had a higher protein content than that of fluid from the lymph spaces of the same limb or than that of edema fluid from dropsical patients.

The complete triple response occurred in areas in which the sensory innervation had been interrupted recently. However, in skin anesthetized by nerve block with cocaine the local red reaction and the wheal occurred as in normal skin, but the spreading flare was absent. Neither did the flare occur in areas where complete degeneration of cutaneous nerves had occurred. For these reasons the flare was explained as an axon reflex resulting in dilatation of adjacent arterioles, but the local dilatation of capillaries and the edema were caused by some mechanism independent of innervation.

The triple response was produced characteristically by various agents. These included histamine, burning, freezing, faradic current, intense light, various acids, alkalis and salts, mustard oil, cantharidin, nettle stings, bites and stings of insects, peptone and foreign proteins. Bacterial toxins produced similar results but with variations in the time factor.

Lewis presented an impressive array of evidence derived from varied experiments which supports the conclusion that this reaction is produced not by the irritant itself but by a substance released from the cells in response to the irritation. The injection of watery extracts of normal human epidermis into the skin produced wheals indistinguishable from those produced by solution of histamine. Numerous analogies were found between this substance and histamine. He concluded that the mechanical stroke or any other form of irritation to the skin produces injury to the deep epidermal cells and that in response to this injury the cells liberate a diffusible substance which acts like histamine on the walls of the capillaries, causing them to dilate and to become more permeable. Lewis could not distinguish this substance from histamine, but lacking absolute chemical identification he spoke of it as H-substance. He stated that whenever the skin displays an acute reaction in the form of the triple response that reaction is provoked by H-substance.

Harris [3] found that histamine is released in a diffusible form following burns made on the skin of mammals. He made physiologic assays for histamine in normal human epidermis and found from 22 to 24 mg. of histamine per kilogram. Kalk [4] and Harmer and Harris [5] corroborated this finding. Histamine has been demonstrated by many

3. Harris, K. E.: Heart **14**:161, 1927.

4. Kalk, H.: Ztschr. f. klin. Med. **109**:118, 1928; Klin. Wchnschr. **8**:64, 1929.

5. Harmer, I. M., and Harris, K. E.: Heart **13**:381, 1926.

workers (Best and McHenry [6]) in similar amounts in tissue of the lung and gastro-intestinal mucosa and in varying amounts in other tissues. Loos [7] produced acute serous inflammation in rabbits' ears by the application of hot water. He extracted histamine from the inflamed ear in eight times the concentration found in the normal ear of the same rabbit. He found also that histamine in a dilution of 1 : 40,000 increased the phagocytic activity of leukocytes in vitro. Other reports have suggested a relationship between histamine and phenomena associated with injury to tissue.

Dale [8] reviewed and corroborated Lewis' investigations and conclusions and stated:

> If H-substance is not histamine it is a substance which immediately yields it when the simplest and least injurious procedures which we can devise are applied to its extraction from the cells and its isolation for chemical study. . . . We have as good chemical evidence of the presence of histamine in the cells of the body generally, and of its liberation from them under certain conditions, as we have of the existence of adrenalin in the suprarenal medulla, and of its secretion as such into the blood.

Krogh [9] endorsed the conclusion that histamine or H-substance is liberated from the skin of mammals whenever and however the cells are injured and that it affects the capillaries in two particulars: It causes them to dilate, producing local hyperemia, and it increases their permeability, causing local edema and swelling.

Lewis found that both the triple response to any injury and the reaction to a solution of histamine pricked into the skin produced a local increase in temperature. Kling [10] found that the therapeutic application of histamine to the skin by cataphoresis increased the local temperature by 2 or 3 C. Histamine even in high dilution is irritating to sensory nerves and produces pain. This factor plus the increased tension resulting from edema may account for the pain which develops following local injury to cells. The local cutaneous reactions to histamine result in heat, redness, pain and swelling, the cardinal signs of acute inflammation. It is self-evident that three of these are merely the visible evidences of vascular changes.

The observations cited may be summarized as follows: The cells of normal tissues contain some combination of histamine in a nondiffusible form. The amounts of this are greater in tissues which are

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6. Best, C. H., and McHenry, E. W.: Physiol. Rev. **11**:371, 1931.

7. Loos, H. O.: Arch. f. Dermat. u. Syph. **164**:199, 1931; Ztschr. f. d. ges. exper. Med. **75**:463, 1931.

8. Dale, H. H.: Lancet **1**:1235, 1929.

9. Krogh, A.: Anatomy and Physiology of Capillaries, ed. 2, New Haven, Conn., Yale University Press, 1928.

10. Kling, D. H.: Ann. Surg. **99**:568, 1934.

most subject to injuries, such as the skin, the respiratory system and the gastro-intestinal tract. The cells when injured liberate histamine locally in a diffusible form. It affects the adjacent capillaries, causing them to dilate and to become unresponsive to substances or nerve impulses which produce contraction. Also, it increases the permeability of the capillary endothelium, resulting in transudation of plasma which produces edema. If the sensory nerve fibers are intact histamine causes reflex dilatation of neighboring arterioles, thus increasing the flow of blood. The vascular phenomena of inflammation, resulting in dilatation of arteries and capillaries, congestion, edema and swelling, have received an acceptable explanation.

These observations raise the question of what relationship may exist between histamine and the leukocytic phenomena associated with inflammation. This question may best be discussed under general (blood stream) and local leukocytosis. Few studies have been made on the effects of histamine on the leukocytes in the blood. Lieber, Kennedy and I [11] have reviewed the literature and have reported on the effects of histamine administered intravenously and subcutaneously to cats, monkeys and human subjects. Single intravenous injections of from 1 to 2 mg. were followed regularly by a marked increase in the number of polymorphonuclear cells in the blood of cats. The number returned to normal within twenty-four hours. Subcutaneous injections of histamine into monkeys were followed regularly by marked leukocytosis. The effects appeared to vary with the dosage, and the count remained above normal for three or four days. Following the injection of 0.75 mg. the count rose from 5,400 to 18,850 within two hours. Following the injection of 9 mg. the count rose from 5,550 to 57,550 within one hour. In human subjects the effects were much less marked, perhaps because of the small dosage in proportion to the body weight. The intravenous injection of from 0.5 to 1 mg. was followed by a slight increase in the number of polymorphonuclear cells in the blood. Subcutaneous injections of from 2 to 3 mg. produced no significant changes. Injections of 5 mg. produced a moderate increase in the number of polymorphonuclear cells in the blood.

We concluded that the injection of histamine phosphate causes leukocytosis. However, there is a question whether the degree of this relative to the amount injected is proportionate to the leukocytosis associated with extensive inflammation. Such leukocytosis may be due in part to histamine and in part to some other factor associated with inflammation. Or the form in which histamine exists in the tissues may be more effective than is histamine phosphate.

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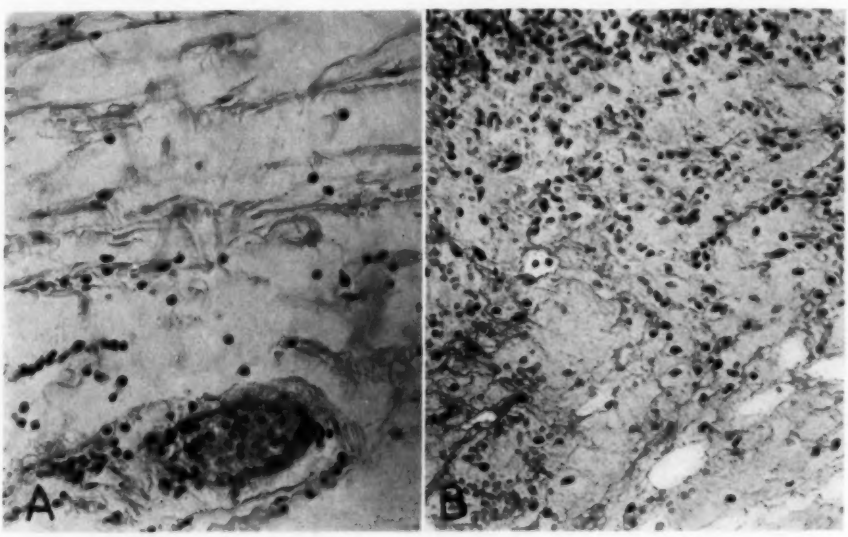
11. Moon, V. H.; Lieber, M. M., and Kennedy, P. J.: Arch. Path. **20**:209, 1935.

Attention is now directed toward the local accumulation of leukocytes in and about areas of injury to the tissues. A mild local burn furnishes conditions suitable for observations on this phenomenon. It is a simple injury uncomplicated by the presence of bacteria or of any foreign substance. No external agent or factor is introduced. The reaction to such an injury must depend entirely on endogenous processes.

EXPERIMENTAL OBSERVATIONS

Experimental burns were made on guinea-pigs. A metal rod 5 mm. in diameter with smooth ends was sterilized and heated in water at 90 C. The end of this rod was held against the skin of the abdomen of a guinea-pig for ten seconds.



Photomicrographs of (*A*) subcutaneous tissue one hour after a burn. Marked edema is present and the migration of leukocytes is beginning. *B* shows subcutaneous tissue eight hours after a burn. Inflammatory edema, migration of leukocytes and diapedesis of red cells are marked. The accumulation of leukocytes in the upper part of the field is just beneath the burned area.

The entire abdomen had been clipped, shaved and sterilized as for a surgical operation. The possibility of infection was minimized by covering the abdomen with a sterile gauze dressing following the burn. A series of such burns was made at intervals on the same guinea-pig, after which sections of the skin were prepared for microscopic study. Within one hour the capillaries and venules were widely dilated in the deep cutaneous and subcutaneous tissues, distinct edema was present, and the migration of leukocytes was beginning (figure). At later periods the leukocytes were progressively more numerous and had wandered away from the vessels. This migration was not uniform in all directions but was from the vessels and toward the burned areas. The evidence indicated that some substance was attracting the leukocytes into the areas of injury. Repetitions of this experi-

ment gave uniformly similar results. Those who have not made a study of acute inflammation, the time factor of which is known definitely, have an imperfect idea of the speed with which the reaction develops in previously normal tissue. The vascular response is immediate; the development of edema begins within a few minutes, and leukocytic migration begins within an hour. Within eight hours all the features of acute inflammation are fully developed. The area is hyperemic and swollen, the tissue fibers are separated by marked edema and a marked leukocytic infiltration is present (figure, *B*).

In another experiment blisters were raised by burning human skin in areas previously sterilized as for a surgical procedure. The mouth of a test tube 5 mm. in diameter filled with water at 80 C. was held against the skin for five seconds. A characteristic hyperemic reaction with surrounding flare developed immediately. Shortly the edematous swelling caused separation of the superficial epithelial layer, and a bleb was formed. Counts of the leukocytes in such blister fluid were made at varying intervals following such burns. A few representative counts on such fluid, together with the elapsed time following the burns, are given in the following tabulation.

Leukocytes	Elapsed Time, Hours
2,750	3
4,700	3
8,600	3
2,400	6
12,650	6
17,350	6
21,200	24
27,650	24

This migration of leukocytes into blister fluid apparently was not due to bacteria. The areas were sterile, and no bacteria were found in the fluid. Neither was it due to other extraneous agents, for no foreign substance of any kind was introduced. One cannot escape the conclusion that the substance which attracted leukocytes was derived from injured cells.

Others have made observations on leukocytosis following burns. Pack [12] reported that what he called "burn toxin" was chemotactic for leukocytes. Schattenberg and Harris [13] demonstrated that local leukocytosis resulted when rabbits' ears were immersed in water at a temperature of 44 C. The untreated ears of the same rabbits were used as controls. Pack, Underhill,[14] Askanazy [15] and others have attested the fact that generalized leukocytosis follows extensive superficial burns.

12. Pack, George T.: Arch. Path. **1**:767, 1926.

13. Schattenberg, H. J., and Harris, W. H.: Proc. Soc. Exper. Biol. & Med. **29**:269, 1931; **29**:1052, 1932.

14. Underhill, F. P.; Kapsinow, R., and Fisk, M. E.: Am. J. Physiol. **95**:315, 1930.

15. Askanazy, M., in Aschoff, L.: Pathologische Anatomie, ed. 7, Jena, Gustav Fischer, 1928, vol. 1, p. 69.

Locke [16] made studies of the blood immediately following such burns in ten patients. Marked leukocytosis was present in every case. The counts ranged between 10,000 and 50,000 within two and one-half hours. He found that marked leukocytosis appeared within an hour and that it was progressive and proportionate to the severity of the burn. Regularly in fatal cases the count was above 50,000 before death. I know of no other condition capable of producing so high a leukocyte count in so short a time. It is as if a sudden call to arms had roused myriads of defenders from their tents. The question is whether the alarm was telegraphed by way of nerve fibers or was carried to the bone marrow and other distant parts by the subtle means of a substance released by injured cells.

The evidence thus far indicates that systemic leukocytosis follows the injection of histamine in experimental animals and in man, that systemic leukocytosis follows extensive superficial burns and that leukocytes are attracted toward burned areas by some substance released locally as a result of the injury. The question is whether that substance is histamine.

Wolf [17] reported that a 0.000025 per cent solution of histamine was strongly chemotactic. However, Bloom,[18] Paul [19] and others were unable to find evidence that histamine has any chemotactic effect. Following the technic which Wolf described and with modifications of it in vitro I did not note increased migrations of leukocytes toward inert substances containing varying concentrations of histamine. Experiments were then devised to secure further evidence on this point in vivo.

In one series of experiments cylindric bits of elder pith of uniform size, 4 by 10 mm., were first soaked in ether, in alcohol and in salt solution for twenty-four hours each to remove any soluble substances. These were then saturated with physiologic solution of sodium chloride containing histamine phosphate in a 1:10,000 solution and were implanted in animal tissues through a canula by the method devised by Konzelmann and me.[20] Some were introduced into the peritoneal cavity and others into the loose subcutaneous areolar tissue. In every instance a bit of elder pith saturated with physiologic solution of sodium chloride was similarly implanted as a control. Plugs saturated with histamine were implanted in nine monkeys, eight cats and four guinea-pigs. After from six hours to twenty-four hours the animals were killed and the reaction about the histamine pith was compared with that of the control. In every instance there was a marked zone of congestion about 2 cm. in diameter surrounding the pith saturated with histamine. There was none about the controls. The capillaries and venules in the former areas were markedly distended, congested and prominent as compared with those around the controls. Microscopic examination revealed numer-

16. Locke, E. A.: Boston M. & S. J. **147**:480, 1902.
17. Wolf, E. P.: J. Exper. Med. **35**:375, 1921; **37**:511, 1923.
18. Bloom, W.: Bull. Johns Hopkins Hosp. **33**:185, 1922.
19. Paul, J. R.: Bull. Johns Hopkins Hosp. **32**:20, 1921.
20. Moon, V. H., and Konzelmann, F. W.: Arch. Path. **10**:587, 1930.

ous leukocytes about both test and control piths. There was no evidence of active invasion of the pith by cells, and leukocytes were apparently as numerous about the control piths as about the ones containing histamine.

In another series of animals histamine was mixed with neutral 2 per cent agar and was injected subcutaneously. Injections of agar without histamine were used as controls. Congestion was more marked about the histamine and agar, but leukocytosis was equally marked about each.

These experiments in vivo indicated that histamine produces marked hyperemia, especially of the capillaries and venules, when introduced into living tissue. There was complete absence of evidence that histamine phosphate attracts leukocytes locally. In each of the implantation experiments some degree of local injury to the tissue was produced. The evidence indicates that some product of cellular injury other than histamine is responsible for the local attraction of leukocytes. These interpretations are in agreement with the conclusions of Morgan [21] from similar experiments that the chemotactic substance is not histamine but is some other product of injury to the tissue.

COMMENT

A wealth of literature has resulted from efforts to discover what functions histamine serves in the physiology of normal tissues. There is agreement that histamine in very low concentration causes capillaries and venules to dilate and to become more permeable. It appears that the immediate vascular reaction to local injury to the tissue—the vascular phenomena of beginning inflammation—results from this action. The experiments by Lieber and me indicated that large amounts of histamine such as might be released from extensive injuries may cause a systemic mobilization of leukocytes. It appears that histamine produces other systemic phenomena associated with inflammation. Weiss, Robb and Ellis [22] made studies on various manifestations following slow continuous injection of histamine into human subjects. The quantities given were not sufficient to produce such circulatory disturbances as follow the sudden administration of histamine in large amounts. They noted an increase in the cardiac rate; the cardiac output was increased 20 per cent, and the basal metabolic rate was increased from 15 to 50 per cent. Concurrent observations on body temperature would be of interest had they been recorded.

My experiments indicated that the substance which attracts leukocytes into areas of injury to the tissue is derived from injured cells. They also indicated that this attraction is due to some other substance than histamine. Krogh suggested that other products of cellular disin-

21. Morgan, J. R. E.: Arch. Path. **18**:516, 1934.

22. Weiss, S.; Robb, G. P., and Ellis, L. B.: Arch. Int. Med. **49**:360, 1932.

tegration are chemotactic. Lewis admitted that there may be more than one H-substance, some of which may have other properties than those of histamine. It would not be strange if the same substance which attracts leukocytes locally should also be effective in producing systemic leukocytosis.

The deposition of fibrin in areas of inflammation was not made the subject of study. It was shown by Lewis that the edema fluid in wheals is similar in composition to blood plasma. Such fluid contains fibrinogen and other factors necessary to the formation of fibrin in the presence of injured cells. Apparently the presence or absence of fibrin in inflammation is conditioned on the degree of increased capillary permeability. If this is increased only slightly the edema contains less plasma proteins, and fibrinogen may not be present in it.

All the phenomena of acute inflammation are explainable as local reactions to substances released by injured cells. In the language of Lewis, the agent that alarms the garrison and mobilizes the vascular defenses is a chemical agent derived from the tissues. The perfection of this mechanism is such that the defense is organized immediately and at every threatened point; it is arranged and carried through locally, being independent of higher systems of control (nervous) and of distribution (cardiovascular). It develops and runs its characteristic course even in denervated areas.

Complex animal organisms are endowed with several physiologic mechanisms which are operative only in emergencies. These are protective and are automatically activated by some factor inherent in the emergency itself. Examples of such mechanisms may be seen in the increased discharge of epinephrine into the blood in response to pain, fear or other emotions, the coagulation of blood following injuries to the walls of the vessels, and the development of immunity as a reaction to certain infections. The inflammatory reaction may best be interpreted as belonging in this group of physiologic mechanisms. It is the local reaction of vessels and cells (leukocytes) to an injury. It is protective in character and purpose, designed to lessen the effects of the injury and to facilitate repair and restitution.

A mechanism by which injured tissues may themselves initiate a local and systemic defensive reaction independent of nerve impulses and of remote control is admirably adapted to the purposes of defense and repair.

CONCLUSIONS

The local vascular and cellular phenomena of acute inflammation result from the liberation of substances from injured cells.

One such substance, which apparently is some combination of histamine, produces the vascular reactions resulting in congestion,

capillary dilatation and permeability, edema and local elevation of temperature.

Systemic leukocytosis results from the injection of histamine phosphate into animals. Histamine released from extensive areas of injured tissue is probably a factor in producing the resulting leukocytosis.

A substance released from injured cells attracts leukocytes to the area of injury. This same substance may also be effective in systemic leukocytosis. Apparently this substance is not histamine.

There is evidence that increase in the metabolic rate and in the rapidity of circulation follows the injection of histamine. This may be a factor in the systemic reactions which accompany extensive inflammation.

LATE CHANGES IN THE LIVER INDUCED BY MECHANICAL OBSTRUCTION OF THE HEPATIC VEINS

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AND
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Numerous methods have been employed in attempts to produce experimental cirrhosis of the liver. As shown in the recent review of the subject by Moon,[1] most investigators in this field have used some poison which, in most instances, caused varying degrees of fibrosis rather than typical cirrhosis. Permanent occlusion of the hepatic veins by obliterating endophlebitis, reviewed by Hess[2] in 1905, by Meyer[3] in 1918 and by Satke[4] in 1929, induces varying degrees of fibrosis of the liver. No one appears to have studied the late effects of temporary occlusion of the hepatic veins, although Simonds and Callaway[5] have reported the changes in the livers of dogs during the first seven days following such operative procedure. This paper is a report of the anatomic alterations and the functional changes in the livers of twelve dogs following mechanical obstruction of the hepatic veins by the method described by Simonds and Brandes[6] for periods of from ten to fifty minutes. The animals were put to death at intervals from the seventh to the sixtieth postoperative day.

OBSERVATIONS

The dogs were selected for these experiments without regard to age or sex. Pentobarbital sodium given intravenously in doses of from 30 to 35 mg. per kilogram of body weight was used as an anesthetic in all experiments except the last two, in which morphine, atropine and ether were employed. The mechanical occlusion of the hepatic veins was maintained for thirty minutes in all except three dogs. In these three animals the periods of occlusion were ten, eighteen and fifty minutes, respectively. During obstruction of the hepatic veins the liver became

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1. Moon, V. H.: Arch. Path. **18**:381, 1934.
2. Hess, A. F.: Am. J. M. Sc. **130**:986, 1905.
3. Meyer, O.: Virchows Arch. f. path. Anat. **225**:213, 1918.
4. Satke, O.: Deutsches Arch. f. klin. Med. **165**:330, 1929.
5. Simonds, J. P., and Callaway, J. W.: Am. J. Path. **8**:159, 1932.
6. Simonds, J. P., and Brandes, W. W.: Am. J. Physiol. **72**:320, 1925.

greatly enlarged, cyanotic, tense and firm. Immediately following release of the veins it rapidly decreased in size and again had the appearance and feel of a normal liver. As soon as the dogs recovered from the immediate effects of the operation all except dog 10 ate heartily and appeared to be in good health until put to death.

Hepatic Function.—Bromsulphalein tests of hepatic function were made on all animals. From 2 to 4 mg. of the dye per kilogram of body weight was given intravenously, and blood specimens treated with oxalate were collected fifteen and thirty minutes after administration. We have considered a 15 per cent retention of bromsulphalein in the plasma at fifteen minutes when a 4 mg. dose was employed to be the maximal normal retention in the dog. In only one instance (dog 15) did we observe a significant retention following operation. Twenty-four hours after operation, with a dose of 4 mg. per kilogram of body weight, there was from 50 to 60 per cent retention of bromsulphalein at fifteen minutes and 20 per cent retention at thirty minutes. Seventy-two hours after operation, 20 per cent of the dye had been retained at fifteen minutes and a mere trace at thirty minutes. The lipase test (see next paragraph) was negative in this dog. The pathologic changes in the liver when the dog was killed with chloroform on the thirty-fifth postoperative day were no more marked than in other animals in group 1 described later.

Blood Lipase.—The blood lipase was investigated in eight dogs. The technic employed differed from that suggested by Cherry and Crandall [7] only in that a control test was made with each determination. These authors stated that both in dogs and in man lipase capable of splitting olive oil appeared in increased amounts in the blood only when pathologic changes were present in the liver and pancreas. Our results have been expressed in the number of cubic centimeters of twentieth-normal sodium hydroxide required for neutralization of the fatty acid liberated by the lipase. A reading of 0.2 cc. of twentieth-normal sodium hydroxide has been considered the maximum of experimental error and the maximum normal lipase content of the blood. No significant rise was found in three dogs (6, 14 and 15), while in five there was a distinct rise following operation (table). The titer of the lowest maximal increase of blood lipase in these five dogs was 0.8 cc. of twentieth-normal sodium hydroxide in dog 8; the highest was 6.65 cc. in dog 13. The highest titers of blood lipase were noted during the first five days following operation. In four dogs the blood lipase returned to normal levels by the tenth postoperative day, while in one animal (13) it was not investigated after the fourteenth postoperative day, although at that time it had not returned to normal. If the present conception of the significance

7. Cherry, I. S., and Crandall, L. A.: Am. J. Physiol. **100**:266, 1932.

of this enzyme that splits olive oil is correct, these five animals should be considered as having had either preoperative or postoperative pancreatic or hepatic damage. Three of these dogs (8, 10 and 11) were killed on the seventh, fourteenth and ninth postoperative days, respectively, and belong in group 1; the other two (9 and 13), each killed on the sixtieth day after operation, were in group 2. Inasmuch as the increase in blood lipase occurred in the first ten days after occlusion of the hepatic veins, it is possible that the changes in the liver cells characteristic of group 1 may be associated with the increase of lipase in the blood. This supposition is, in a measure, in harmony with the observations of Whipple.[8] The three dogs with normal blood lipase belong in group 2.

The presence of an olive oil-splitting enzyme was demonstrated in the blood of dog 10 before operation. Whether the yellowish areas of fatty change in the liver observed at operation and present as "fatty infarcts" (Cesaris Demel,[9] Marras [10]) in sections had any bearing on

Results of Study of Blood Lipase in Dogs with Experimental Obstruction of Hepatic Veins

	Cubic Centimeters of Twentieth-Normal Sodium Hydroxide Required to Neutralize the Acid Liberated Lipase														
	Days Before Operation		Days After Operation												
Dog	2	1	1	2	3	4	5	6	7	8	9	10	11	12	13
8	....	0.0	0.80	0.40	0.00	0.10	0.00	....	....	....	....	....	....	....	....
9	....	0.1	1.15	1.25	0.50	0.35	0.60	0.30	0.30	0.60	0.10	0.00	0.05	0.00	....
10	0.50	1.30	0.80	0.50	2.40	1.75	1.40	0.60	0.80	0.85	0.80	0.80	....	....	....
11	....	0.00	2.80	2.15	2.25	0.40	0.30	0.20	....	....	....	....	....	....	....
13	0.0	0.0	0.30	5.80	6.65	6.10	3.40	0.90	1.40	1.10	1.20	1.00	1.20	0.90	0.60

the preoperative positive titer is uncertain, for we have noted the presence of lipase in the blood of a few supposedly normal dogs examined at random. This dog was seized with uncontrollable generalized convulsions and was put to death fourteen days after operation. These convulsions could not be adequately explained. The blood showed 95 mg. of sugar per hundred cubic centimeters. Unfortunately the blood calcium was not determined. The parathyroids, however, were slightly enlarged, compact and free from intercellular fat. It is probable, therefore, that the convulsions were not related to tetany. The changes in the liver were those described in group 1 in a subsequent paragraph and were apparently no greater than those in other dogs in this group which did not have convulsions. The pancreas and kidneys were essen-

8. Whipple, G. H.: Bull. Johns Hopkins Hosp. **24**:357, 1913.
9. Cesaris Demel, A.: Pathologica **24**:332, 1932.
10. Marras, S.: Pathologica **25**:798, 1933.

tially normal. Examination of the brain for Negri bodies and other changes revealed nothing that explained the convulsions. They may, therefore, have been associated with hepatic insufficiency.

Hepatic Changes.—These dogs can be divided into two equal groups of six animals each on the basis of the type of changes in the hepatic cells:

1. In group 1 the hepatic cells were swollen and granular. In only two dogs (10 and 12) did sections stained with sudan III show appreciable amounts of fat. The nuclei were either normal in appearance or were pale or pyknotic. Occasionally one or more cells were without nuclei. The sinusoids were, in general, narrowed but distinctly visible. In all livers in this group there were scattered, irregular, usually small areas in which the sinusoids of one or more lobules were distended with blood. This type of change was more common in the earlier stages, although it was present in a dog killed on the fifty-second postoperative day.

2. In group 2 the hepatic cells were enormously swollen, their outlines very distinct, their cytoplasm clear and foamy, and their nuclei usually small and hyperchromatic or, sometimes, absent (fig. 1). This is believed to be hydropic degeneration or intracellular edema. Fat was present in the liver cells in dog 13 only, the animal which had the highest titer of lipase. The sinusoids were collapsed and distinguished only with difficulty. The lobules were practically bloodless except for an occasional isolated red blood cell squeezed in a ring of hepatic cells. The sections had the appearance of a very fine mosaic, and the general histologic architecture was greatly obscured but still recognizable. This type of change was observed chiefly in the later stages—from the fourteenth to the sixtieth postoperative day.

The liver weight-body weight ratios varied from 2.23 per cent to 3.96 per cent, the average for the twelve dogs being 3.092 per cent. In five cases it was less than the average reported by Junkersdorf [11] (3 per cent) and Simonds and Brandes [12] (3.03 per cent) for normal dogs, while in seven cases it was greater than the normal average. The average ratio in group 1 was 2.82 per cent with 60 per cent below normal; in group 2 the average ratio was 3.24 per cent with 66 per cent above normal. No relationship existed between the length of time the veins were constricted and the ratio of the liver weight to the body weight. The highest ratio, 3.96 per cent, was in a dog put to death fourteen days after operation. The ratios in two dogs which survived sixty days were 3.22 per cent and 3.78 per cent, i. e., above normal. Simonds and Callaway [5] found that in dogs killed from a few hours

11. Junkersdorf, P.: Arch. f. d. ges. Physiol. **200**:443, 1932.
12. Simonds, J. P., and Brandes, W. W.: Arch. Path. **9**:445, 1930.

to seven days after operation the liver weight-body weight ratios ranged from 3.57 per cent to 3.96 per cent with an average of 3.77 per cent.

Accumulations of cells similar to those described by Simonds and Callaway [5] were noted in the sinusoids in all cases. Some of these cells contained an iron-bearing pigment. Occasionally a few liver cells adjacent to or within the larger accumulations were necrotic, and thus these areas had the characteristics of the focal necrosis of typhoid fever described by Mallory.[13] At sixty days these cell masses in the sinusoids were rarely seen, probably because, their mission of phagocytosis having been fulfilled, they disintegrated.

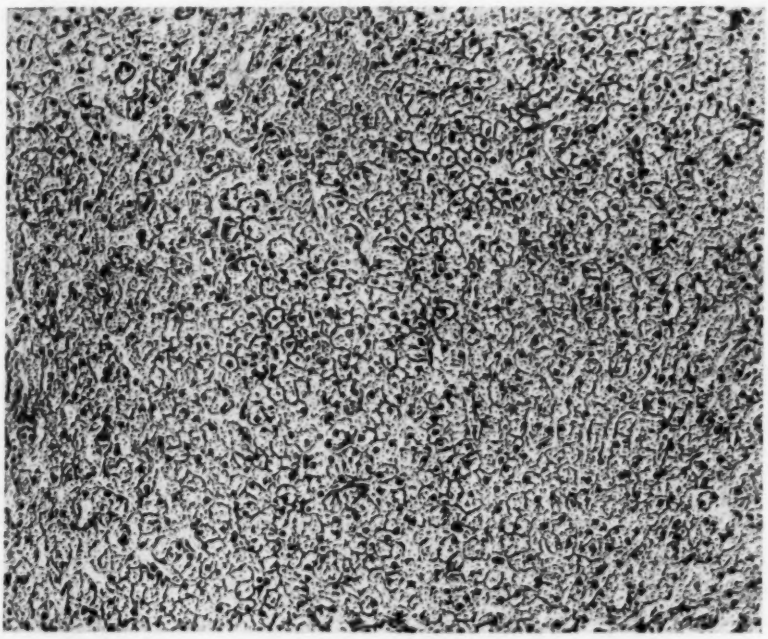

Fig. 1.—Hydropic degeneration or intracellular edema in dog 9 on the sixtieth postoperative day; × 145. Note the appearance of a fine mosaic, the distinctness of the cell outlines and the blurring of the normal histologic architecture.

A dilatation of the lymphatics around the sublobular, and sometimes about the portal, veins was noted in all twelve dogs; it was less prominent after the twentieth postoperative day. This phenomenon was also described by Simonds and Callaway.[5] In many instances the dilated lymphatics contained a pinkish-staining hyaline material. Similar homogeneous hyaline material was also present in the lumens of a varying number of central, sublobular and portal veins.

13. Mallory, F. B.: J. Exper. Med. **3**:611, 1898.

From the seventh to the twentieth day following operation accumulations of mononuclear cells were present around the central veins. The nuclei of most of these cells were large, round, oval or indented and stained well with hematoxylin. Among these large mononuclear cells were occasional lymphocytes and polymorphonuclear leukocytes. From about the twentieth postoperative day onward definite fibrous thickening of the walls of the central veins was evident. This became more marked as the postoperative period lengthened (fig. 2 *A* and *B*). The connective tissue cells were frequently arranged radially about the stenosed central veins (fig. 2 *A*). This was the only evidence of fibrosis in the livers of any of these dogs except for a slight increase of periportal connective tissue with moderate lymphocytic infiltration in dog 14 (group 1), killed on the fifty-second postoperative day. We have frequently observed an equal amount of periportal fibrosis in other dogs used in acute experiments.

Changes in Other Organs.—The pathologic changes in other organs of these twelve dogs were relatively insignificant. Hyperemia of the spleen was present only in dog 3, in which the hepatic veins were constricted for only ten minutes and which was killed on the twentieth day after operation. In the other eleven dogs the spleen contained little blood; the pulp was moderately fibrotic, and hemosiderosis, not uncommon in old dogs, varied in amount. The pancreas was essentially normal in each animal in this series. The adrenals were normal except in dog 10, in which they were uniformly enlarged. The thyroid of this animal contained an adenoma, and its parathyroids were moderately enlarged, compact and free from intercellular fat.

The condition of the kidneys in these animals is important in view of the observations of Helwig and his co-workers,[14] who found serious renal changes in patients who had suffered severe, usually traumatic damage to the liver. In our dogs the glomeruli showed no noteworthy changes, although they varied in the amount of blood in the capillaries and the completeness with which they filled the capsular spaces. In a few dogs the epithelium of the proximal convoluted tubules was moderately swollen and granular, and the lumens contained varying amounts of granular material. In no case were casts present.

COMMENT

From these experiments it is evident that the dog's liver can withstand complete or almost complete stagnation of its circulation for periods of from thirty to fifty minutes, with relatively slight structural changes and functional disturbances. Using a method very different

14. Helwig, F. C., and Orr, T. S.: Arch. Surg. **24**:136, 1932.

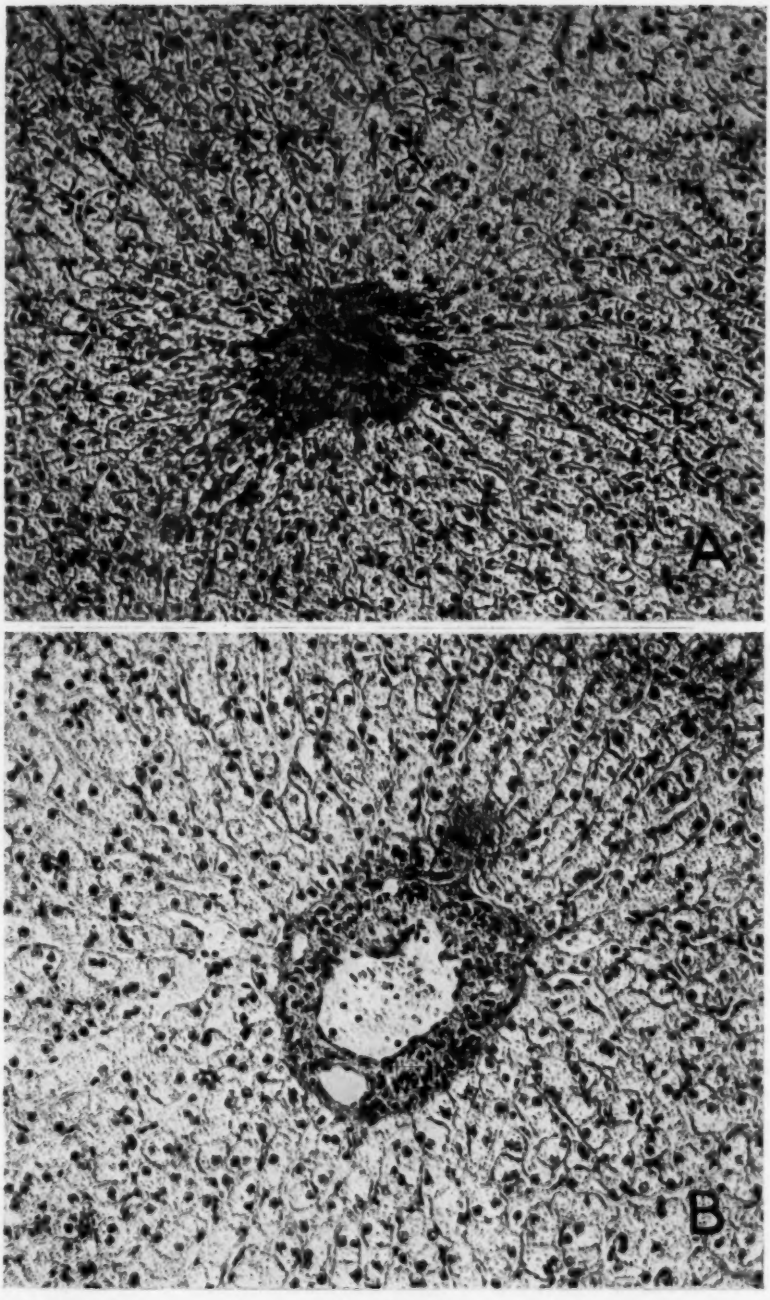

Fig. 2.—*A*, fibrosis about a central vein and radial arrangement of the connective tissue cells in dog 9; × 225. *B*, fibrosis about a central vein in dog 13 on the sixtieth postoperative day; × 225. Note the presence of channels in the fibrous tissue apparently for the passage of blood from the sinusoids to the vein. *A* and *B* also show hydropic degeneration or edema of the hepatic cells.

from ours, Chandler [15] arrived at the same conclusion. This is in strong contrast to the effects of temporary stoppage of the circulation in other organs. Thus Gildea and Cobb [16] found that ligation of the arteries of the brains of cats for ten minutes resulted in complete cessation of function of the ganglion cells with histologically demonstrable degeneration of these cells. Chandler [15] reported that deprivation of oxygen for two hours causes almost complete necrosis of the epithelium of the renal cortex. McEnery, Meyer and Ivy [17] found that clamping of the renal vessels for from thirty to sixty minutes caused degenerative changes in the kidneys which often progressed to "the formation of a small white kidney" in dogs that survived for from ten days to seven months. The results varied with the extent of the collateral circulation.

This difference in resistance to anoxemia between the liver and other organs cannot be due to lack of specialization of the hepatic cells, for the liver possesses a greater number and variety of functions than any other organ of the body. Several factors may combine to produce this relative immunity of the liver to anoxemia. In the first place the hepatic cells are accustomed to a blood supply with a low oxygen content. Burton-Opitz [18] has calculated that the total blood flow through the liver of the dog is 84 cc. per minute for 100 Gm. of liver. Of this, the portal vein furnishes 59 cc. and the hepatic artery 25 cc. Of the total blood supply of the liver, approximately 70 per cent is venous and 30 per cent arterial. Normally, arterial blood contains 18.5 cc. of oxygen per hundred cubic centimeters and is 95 per cent saturated; venous blood has 15 cc. of oxygen and is about 70 per cent saturated (Wright [19]). The mixed blood in the hepatic sinusoids therefore contains only 16 cc. of oxygen per hundred cubic centimeters and is only 78 per cent saturated. It is, thus, much more like venous than arterial blood. Cells which are accustomed to such a blood supply might well be expected to withstand stagnation of the circulation through the organ for a considerable time.

The liver normally uses relatively little oxygen. Winterstein [20] has presented evidence that the liver of the cat uses 1.1 cc. of oxygen per hundred grams per minute. The kidney uses nearly 2.5 times, and

15. Chandler, L. R.: Proc. Soc. Exper. Biol. & Med. **18**:24, 1920.

16. Gildea, E. F., and Cobb, S.: Arch. Neurol. & Psychiat. **23**:876, 1930.

17. McEnery, E. T.; Meyer, J., and Ivy, A. C.: J. Lab. & Clin. Med. **12**:349. 1927.

18. Burton-Opitz, R.: Quart. J. Physiol. **4**:113, 1911.

19. Wright, Sampson: Applied Physiology, New York, Oxford University Press, 1926, p. 267.

20. Winterstein, H., in Bethe, A.; von Bergmann, G.; Embden, G., and Ellinger, A.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1929, vol. 9, p. 541; cited by Weil, A.: Textbook of Neuropathology. Philadelphia, Lea & Febiger, 1933, p. 76.

the brain about 9 times, that amount. Although the liver requires and uses little oxygen, it does not possess the power of anaerobic respiration with glycolysis and formation of lactic acid, as shown by Warburg.[21]

Furthermore, during mechanical obstruction of the hepatic veins the outflow from the thoracic duct is increased 2.5 times (Simonds and Brandes [22]). There is reason to believe that much of this increase is due to augmented filtration of fluid in the liver. This increased flow of lymph will mechanically remove some of the waste products that cannot be carried away by the blood while the outflow from the liver is obstructed.

Certain of the normal functions of the liver, such as detoxication, deamination, formation of urea and glycogenic activity, may be factors in protection of the hepatic cells against the effects of anoxemia.

Mechanical constriction of the hepatic veins for from thirty to fifty minutes produces three results that might well do permanent damage to any other organ, namely: maximal distention of the sinusoids and veins, anoxemia and retention of the waste products of cell activity during the period of constriction. Six of our dogs showed evidence of temporary disturbance of hepatic function. In one animal there was retention of from 50 to 60 per cent of bromsulphalein at fifteen minutes, twenty-four hours after operation. In five, there was an increase of blood lipase lasting from two to thirteen days. One dog was killed on the fourteenth postoperative day because of uncontrollable generalized convulsions which, because they could not be explained on any other basis, were thought to be related in some way to hepatic insufficiency.

Two types of progressive, or at least continued, degenerative processes were observed. In one group the hepatic cells were swollen and granular as in ordinary parenchymatous degeneration. This change was still quite definite in two dogs killed thirty-five and fifty-two days, respectively, after operation. In the second group the liver cells were enormously swollen, and their cytoplasm was clear and foamy in appearance. This change was marked in three dogs, one of which was killed thirty-seven, the other two, sixty days, after operation. The hepatic cells were so swollen that the sinusoids were completely collapsed and, from the sections, the liver appeared to be almost bloodless. Ravdin [23] illustrates, without comment, such a change in the liver of a dog in which the common duct had been ligated.

The conditions observed by us in these dogs differed in several significant respects from those described by Simonds and Callaway [5] from twenty-four to seventy-two hours and seven days after mechanical con-

21. Warburg, Otto; Posener, K., and Negelein, E.: Biochem. Ztschr. **152**:309, 1924.

22. Simonds, J. P., and Brandes, W. W.: J. Immunol. **13**:11, 1927.

23. Ravdin, I. S.: J. A. M. A. **93**:1193, 1928.

striction of the hepatic veins. In the earlier stages many lobules were flooded with blood, especially in their central portions. This stasis later disappeared almost completely and only an occasional lobule was found filled with blood. The intrasinusoidal cell masses so numerous in the first week also disappeared, for they were rare in the livers of those dogs which survived for periods of from fifty-two to sixty days. The average ratio of liver weight to body weight, although still above normal in group 2, was lower than that in Simonds and Callaway's series of animals. The hyaline thrombi in the central and sublobular veins also vanished with time. Swelling and granulation of the hepatic cells continued occasionally at least to the fifty-second postoperative day. But after the twenty-fifth day hydropic degeneration or edema of the hepatic cells was more common. We are unable to offer a satisfactory explanation for the continuance of this change.

In spite of these progressive or continued degenerative changes there was nothing resembling cirrhosis of the liver. The only increase in connective tissue occurred about the central veins where the mechanical effects of distention were most severe during constriction of the hepatic veins. This differs from the central fibrosis frequently observed in cases of chronic passive hyperemia of the liver. We have been unable to find this condition described in the literature. The process appears to begin between the fourteenth and twentieth days with an accumulation of large cells containing oval or indented nuclei immediately around the central veins. Later the central vein is found to be surrounded by a thick ring of connective tissue cells which are sometimes arranged radially as in figure 2 *A* and sometimes more or less concentrically. The radial arrangement appears to cause stenosis of the vein. When the connective tissue occurs in irregularly concentric layers, the vein is patent and spaces apparently for the passage of blood are present in the fibrous wall, as shown in figure 2 *B*.

SUMMARY

The livers of twelve dogs in which the hepatic veins had been mechanically constricted for periods of from ten to fifty minutes presented the following changes when examined from seven to sixty days after operation:

(*a*) Swelling and granulation of the hepatic cells as in parenchymatous degeneration were more frequently observed in the earlier stages but were still present in two dogs on the thirty-fifth and fifty-second postoperative days, respectively.

(*b*) Extreme swelling of the hepatic cells from either hydropic degeneration or intracellular edema, with apparently complete collapse of the sinusoids, although occasionally present even before the seventh

day, was more characteristic of the later stages and was marked in two dogs on the sixtieth postoperative day.

(*c*) The ratio of liver weight to body weight was greater in the second than in the first group.

(*d*) The hyperemia, the dilatation of the lymphatics accompanying the sublobular veins and the intrasinusoidal cell masses, so prominent in the very early stages, gradually disappeared with lapse of time.

(*e*) Fibrosis of the walls of the central veins was characteristic of the later stages. This change does not appear to have been previously recorded.

In only one dog was there retention of bromsulphalein, and this was observed only once, twenty-four hours after the operation.

The titer of the blood lipase was increased in five of eight dogs studied. The titer usually returned to normal by the fifth postoperative day, but in one animal it was still above normal on the fourteenth day.

One dog was killed quickly with ether on the tenth postoperative day because of uncontrollable convulsions which could not be satisfactorily explained. Because of the presence of numerous "fatty infarcts" in the liver (also observed at the time of operation), it was thought that the convulsions were in some way related to hepatic insufficiency.

Case Reports

ACUTE VALVULAR ENDOCARDITIS IN THE NEW-BORN

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The purpose of this paper is to record the microscopic picture of an active valvular endocarditis in the new-born. No attempt is made to explain its origin. After reviewing the literature on the subject, we have come to the conclusion that active fetal endocarditis must indeed be a rarity.

REVIEW OF THE LITERATURE

Ribbert[1] was unable to find that a fresh lesion of the ulcerative or verrucous valvular type had ever been seen in the fetus or in the new-born infant. He mentioned the cases of Fischer[2] and Kockel,[3] and pointed out that the changes noted by them were old, consisting of thickening or shrinkage of the valves with no direct evidence of an inflammatory process. Ribbert's contention was that these changes might well be the result of an inflammatory lesion which had run its course, or that they might be congenital malformations of the valve; he believed that the latter was the more likely. Several further cases which are recorded in the literature fall into the same category, especially those reported by Loeser,[4] Ludwig,[5] Dissmann[6] and Sawalischin.[7] In all these cases, no definite claim was made that fetal endocarditis was the cause of the changes observed. However, the possibility was suggested in each case.

Ayrolles,[8] Boinet[9] and Ganeff,[10] in their case reports, gave fetal endocarditis as the etiologic factor in the changes seen. Ayrolles reported the case of a boy, born at term, weighing 2,790 Gm., who lived for four days, became suddenly extremely cyanotic, and died. The mother gave a history of chronic osteomyelitis of the left femur, which began to discharge actively again in the third month of pregnancy. Autopsy of the infant revealed a complete obliteration of the mitral

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1. Ribbert, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 206.
2. Fischer, B.: Frankfurt. Ztschr. f. Path. **7**:83, 1911.
3. Kockel, R.: Verhandl. d. Gesellsch. deutsch. f. Naturf. u. Aerzte **80**:39, 1908.
4. Loeser, A.: Virchows Arch. f. path. Anat. **219**:309, 1915.
5. Ludwig, E.: Cor.-Bl. f. schweiz. Aerzte **42**:921, 1912.
6. Dissmann, E.: Frankfurt. Ztschr. f. Path. **43**:476, 1932.
7. Sawalischin, K.: Ueber angeborene Stenose des Aorten- und Mitralostiums infolge fötaler Endocarditis, Bonn, Emil Eisele, 1908.
8. Ayrolles, P.: Rev. mens. d. mal. de l'enf. **3**:222, 1885.
9. Boinet, M.: Bull. acad. de méd., Paris **53**:172, 1905.
10. Ganeff, cited by Loeser.[4]

ostium and a partly obliterated ductus Botalli. The mitral leaflets presented a light red discoloration, while fine adhesions, which were easily detached, were found between the chordae tendineae. No microscopic description accompanies the report.

The case of Boinet[9] was as follows: A 23 year old woman, pregnant, was brought to the hospital because of cardiac disease; she was extremely dyspneic, had marked edema of the lower extremities and claimed to have had heart disease for the preceding three years following pneumonia. There were mitral insufficiency and pneumonia. The patient miscarried and was delivered of a dead fetus at approximately six months; the mother died, and autopsies were made on both. Pneumonia of the right lower lobe was found in the mother. The mitral valve of the mother showed marked fibrosis with stenosis of the ostium. There were several fibrotic nodules on the leaflets. The organs of the fetus were normal except for the heart, which showed a condition analogous to that found in the mother. The mitral valve showed a moderate degree of insufficiency, while several fibrous nodules, the size of millet seeds, were present on the leaflets. Again no microscopic description accompanies the report.

In the case reported by Ganeff,[10] there were "thickening and shrinking of the aorta and a mitral insufficiency."[11] The endocardium was thought to have some localized areas of fresh inflammation. On microscopic examination, the endocardium consisted of dense fibers with few nuclei. The nuclei were seen to increase in number toward the musculature. There was a marked increase in connective tissue. This was considered true verrucous endocarditis and fibrous myocarditis although no distinct evidence of an acute inflammatory process was present.

Conclusive evidence of an existing or a former acute endocarditis seems lacking in each of the last three cases. We are inclined to place them in the same category as those already mentioned.

Capelli[12] more recently reported his observations in the study of sixty-two hearts of human fetuses. He did not encounter acute endocarditis in any case. The slight changes noted by him were either proliferative or degenerative. However, he found thrombi on some of the leaflets. These thrombi were extremely small, consisting of fibrin with a few nuclear elements. Capelli believed that the thrombotic deposits were caused by the changes already present in the leaflets of the valves, or by some toxemia rather than by bacteremia. Similar explanations have been given in the past by Vierordt,[13] Rauchfuss,[14] Dilg[15] and others. They believed that valves with congenital malformations are points of predilection for thrombo-endocarditic lesions.

Abbott[16] stated that "fetal endocarditis, which was believed by the earlier authors to play such an important part in the causation of cardiac anomalies, probably occupies a very minor rôle, being limited to those relatively few cases in which a rheumatic endocarditis is directly transmitted from mother to offspring." Abbott, however, does not mention any cases observed.

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11. Shrinking of the aortic valve is probably meant.

12. Capelli, E.: Pathologica **24**:103, 1932; Sperimentale, Arch. di biol. **87**:129, 1933.

13. Vierordt, H., in Nothnagel, H.: Spezielle Pathologie und Therapie, Vienna, A. Hölder, 1898, vol. 15, p. 225.

14. Rauchfuss, C., in Gerhardt, C.: Handbuch der Kinderkrankheiten, Tübingen, H. Laupp, 1878, vol. 4, p. 132.

15. Dilg, J.: Virchows Arch. f. path. Anat. **91**:193, 1883.

16. Abbott, Maud E., in Osler, W.: Modern Medicine: Its Theory and Practice, edited by Thomas McCrae, Philadelphia, Lea & Febiger, 1927, vol. 4, p. 627.

We were able to find record in the literature of just one such example which was proved by autopsy. The case was reported by Poynton.[17] His description reads: "The child of a mother, the victim of an attack of rheumatic fever in late pregnancy, died on the second day after birth of congenital heart disease. I found exuberant vegetations on the mitral valve forming a relative stenosis, and these vegetations contained numerous diplo-streptococci indistinguishable from the streptococcus rheumaticus; a condition of the mitral valve which pointed to an intrauterine inflammation rather than a true arrest in development." No histologic description was given by Poynton.

REPORT OF A CASE

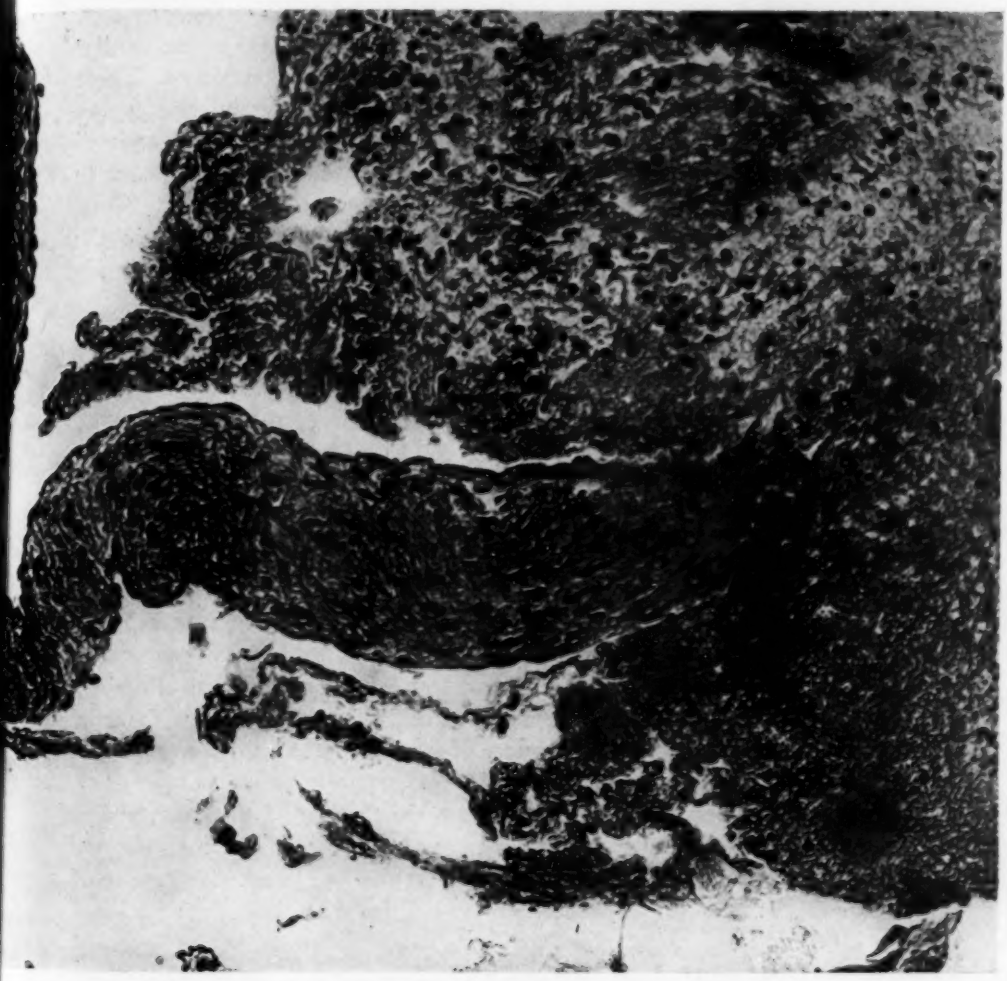
Our case is also one of a fresh verrucous endocarditis on an otherwise normal mitral valve. The lesion was found in a fetus from 6½ to 7 months old, that died one and one-half hours after birth. The mother gave a history of two previous pregnancies which ended in miscarriages, one of from five to six weeks, and the other of five and one-half months; both miscarriages were spontaneous. The medical history of the mother was essentially unimportant. The only mention of an illness elicited was that of a so-called mild influenza, which occurred from three to four weeks prior to delivery. A Wassermann test of the blood was negative. There were moderate tachycardia, tremor and enlargement of the thyroid gland. The delivery was normal. At birth the baby weighed 2 pounds and 9 ounces (1,162.3 Gm.); it was cyanotic and gasping, and died within one and one-half hours.

Autopsy revealed a normally developed female fetus, 38.5 cm. in length. The organs were all grossly normal. A small pinhead-sized, so-called valvular hematoma (blood nodule or sinus) was noted on the mitral valve. Because of a special interest in blood nodules, we sectioned the portion of the leaflet containing the nodule, in series. Approximately fifty sections were available for microscopic study, all stained with hematoxylin and eosin. The remainder of the heart was discarded. No special search was made for endocarditic vegetations on gross examination.

The microscopic study of these sections led to the accidental discovery of a fresh thrombus attached to the leaflet at a point definitely separated from the hematoma. The intervening space was approximately 0.2 mm. wide and showed no pathologic changes; the lining endothelium was intact, and the connective tissue of the leaflet in this area showed no alterations. The vegetation could be studied only in the first few sections of the series. It measured 1 by 0.75 mm. on the slide, but we are unable to tell how large it may have been in its nonexamined portion. Unfortunately, no further material was available. The vegetation consisted of a fine fibrinous network which was diffusely permeated by polymorphonuclear leukocytes and different cells with medium-sized simple nuclei. Some of these nuclei stained very deeply. In addition to the diffusely distributed ones, there were a few densely packed groups of these cells, the densest group being situated near the point of attachment of the vegetation. The endothelial lining of the leaflet was missing at the point of attachment of the vegetation. The nuclei of the valvular tissue beneath the vegetation were swollen; the tissue was homogeneous and stained intensely with eosin. There was no evidence of cellular infiltration or of vascularization of the leaflet in this area. No bacteria could be found. (Only sections stained with hematoxylin and eosin were available.) The myocardium was normal.

17. Poynton, F. J.: Clin. J. **34**:231, 1909.

Microscopic examination of the suprarenal glands, lungs, liver and spleen showed nothing unusual. The hematopoiesis in the liver corresponded to the age of the fetus. Some deep red spherical areas were noted in the brain. They were formed by accumulations of undifferentiated germinal cells and did not represent an inflammatory process. The pancreas was histologically normally developed



The vegetation consists of fibrin, leukocytes and mononuclear elements. The valvular tissue itself for the most part is normal. At the attachment of the vegetation, the connective tissue of the valve is homogeneous, and the nuclei are swollen and deep staining. At the lower edge of the picture, endothelial nuclei are seen protruding from the otherwise normal valve.

for the age of the fetus. However, it contained several large groups of round cells. The largest group of such cells included areas of pancreatic parenchyma and ducts. The other areas of lymphoid cells were well demarcated, lying in the interstitial

tissue, free from the pancreatic parenchyma, and seemed to be lymph follicles rather than an inflammatory tissue. They did not contain germinal centers.

COMMENT

In the presence of an acute inflammatory process on the heart valve of a new-born infant we must attempt to correlate these findings with other findings in the mother or the baby. The only illness of the mother during pregnancy, as mentioned, was a so-called mild influenza. There was no history of rheumatic fever. While, theoretically, one cannot exclude the possibility of a relation between the influenzal attack of the mother and the endocarditis of the fetus, there is no evidence to prove such a relation, or even to make it appear probable.

While we were searching for other inflammatory lesions in the organs of the new-born baby, our attention was caught by the bloody nodules in the brain and the groups of round cells in the pancreas. The cerebral lesion was definitely what older authors called Virchow's encephalitis. Pathologists are practically agreed today that these accumulations of cells are not inflammatory.

The accumulations of round cells in the pancreas might, at first, have been taken for an inflammatory process. However, Nakamura,[18] who made a thorough study of the normal pancreas in ninety new-born and older infants, reported that the condition described occurred in 11 per cent of the cases. He maintained that it is not an inflammatory process but rather is linked to the condition known as status lymphaticus.

Any relation between the blood nodule (valvular hematoma) and the endocarditic lesion is highly improbable. First, the two lesions in our specimen were separated from each other by normal tissue. Furthermore, there have been numbers of careful investigations, with serial sectioning of valvular hematomas. None of these has been the seat of an inflammatory lesion (Wegelin[19]).

We are therefore unable to explain the genesis of this endocarditic lesion. We do not know how often such microscopic lesions may be present on the normal-appearing valves of the new-born. The study of Capelli seems to indicate that they are not frequent.

SUMMARY

A case of acute mitral endocarditis in a premature new-born infant is reported. Its origin cannot be explained. No other inflammatory process was found in the organs of the infant. Acute endocarditis in the new-born seems to be extremely rare.

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18. Nakamura, N.: Virchows Arch. f. path. Anat. **253**:286, 1924.
19. Wegelin, C.: Frankfurt. Ztschr. f. Path. **9**:97, 1911.

CARCINOID OF MECKEL'S DIVERTICULUM

REPORT OF TWO CASES

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AND
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A carcinoid in Meckel's diverticulum is one of the rarest pathologic curiosities. In the literature we were able to find reports of only 2 cases: Hicks and Kadinsky [1] reported the first case in 1922, and Stewart and Taylor [2] reported the second case in 1926. After examination of the specimens, Stewart and Taylor expressed the opinion that there was a strong possibility that the lesion in the first case represented a heterotopia of gastric mucosa rather than a carcinoid. In the literature, besides the reports of the 2 carcinoids, we found records of only 8 sarcomas and 1 carcinoma of Meckel's diverticulum.

We wish to report 2 cases of carcinoid of Meckel's diverticulum which were found in a review of 6,138 cases that came to necropsy at the Mayo Clinic in the years 1923 and 1933 inclusive.

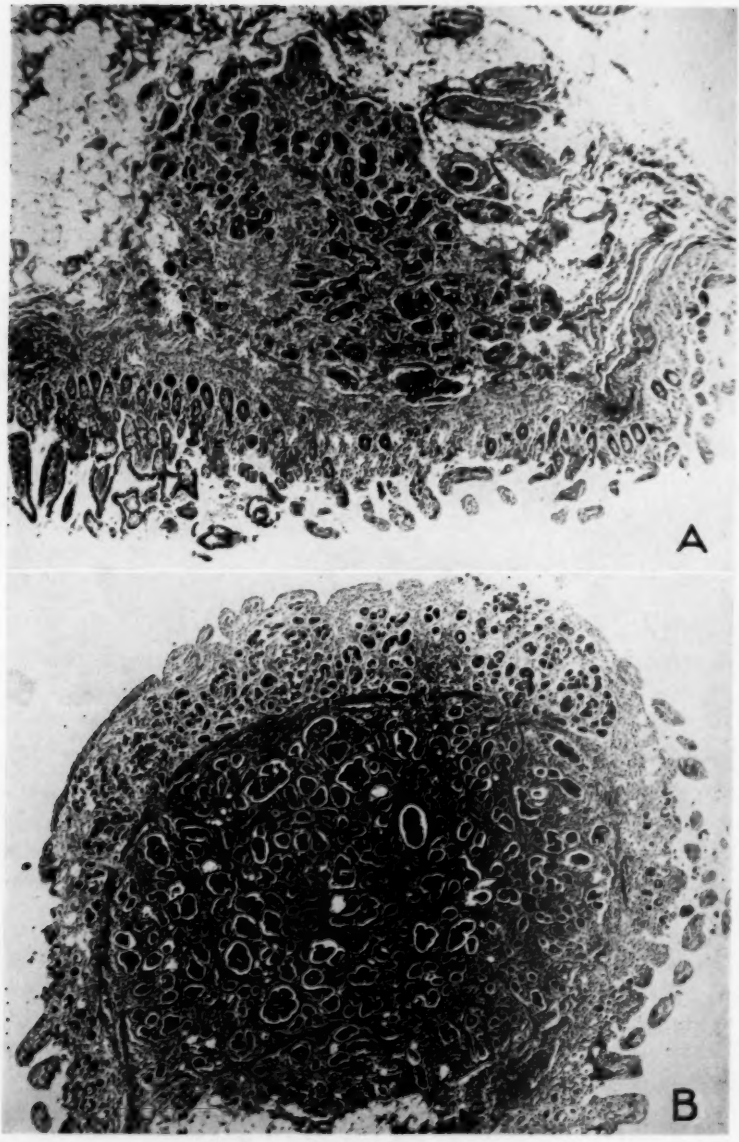
REPORT OF CASES

CASE 1.—The patient was a man aged 54. A small irregularly shaped mass, 4 mm. in diameter, was situated in the submucosa of Meckel's diverticulum (fig. *A*). The overlying epithelium was similar to that of the ileum. The muscularis mucosae was fragmented. The tumor consisted of clusters of deeply staining spheroidal cells, separated by a dense connective tissue stroma. Higher magnification showed that the majority of nests consisted of densely packed hyperchromatic cells, each with a large rounded nucleus, which contained one or more nucleoli. The cellular outline was indistinct. The cytoplasm was granular and stained lightly with eosin. No mitotic figures were seen in any portion of the growth. Other nests of cells differed from the ones just described by the fact that occasional acinic formation was imitated.

CASE 2.—The patient was a man aged 58. A small tumor, 3 mm. in diameter, was situated at the tip of Meckel's diverticulum (fig., *B*). The tumor was similar to that in case 1 in all respects, except that the cells had a tendency to assume more of a rough glandlike formation.

Work done in the Section on Pathologic Anatomy, the Mayo Clinic.

1. Hicks, J. A. B., and Kadinsky, S.: Lancet **2**:70, 1922.
2. Stewart, M. J., and Taylor, A. L.: J. Path. & Bact. **29**:135, 1926.



A, a carcinoid in the submucosa of Meckel's diverticulum; × 32. *B*, a carcinoid in the tip of Meckel's diverticulum; × 25.

COMMENT

That these tumors were carcinoids is established by the typical histologic picture that has been described. The diagnosis was further confirmed by demonstrating the affinity of the cells of both tumors for silver salts.

The carcinoids were first described and separated from the carcinomas by Oberndorfer [3] in 1907. Huebschmann,[4] in 1910, suggested a relationship between the carcinoids and a type of granular epithelial cell of the intestine which had been described previously by Heidenhain,[5] Nicolas,[6] Kultschitsky [7] and Schmidt.[8] Oberndorfer,[9] in 1909, and Gosset and Masson,[10] in 1914, proved this relationship by demonstrating the similarity in staining with chrome and silver salts. Gosset and Masson gave the cell the name argentaffin cell because of this affinity for silver. Whether the argentaffin cell represents an entodermal cell which arises in the intestinal epithelium or an ectodermal cell which has migrated to the intestinal epithelium from the chromaffin tissues of the body is still an unsettled question. The argentaffin cells are found singly or in pairs among the columnar epithelial cells of the entire gastro-intestinal tract. They are more numerous in the distal part of the ileum and in the appendix. Meckel's diverticulum is found in from 2 to 3 per cent of all cases which come to necropsy and is usually found about 90 cm. proximal to the ileocecal sphincter. Although heterotopic tissue which simulates different portions of the gastro-intestinal tract occurs in Meckel's diverticulum, the diverticulum in the majority of instances is lined with epithelium which is characteristic of the ileum. Hence the occasional occurrence of a carcinoid is to be expected.

SUMMARY

The photomicrographs and histologic characteristics of 2 cases of carcinoid of Meckel's diverticulum are presented.

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3. Oberndorfer, Siegfried: Frankfurt. Ztschr. f. Path. **1**:426, 1907.
4. Huebschmann, P.: Rev. méd. de la Suisse Rom. **30**:317, 1910.
5. Heidenhain, R.: Arch. f. mikr. Anat. **6**:368, 1870.
6. Nicolas, A.: Internat. Monatschr. f. Anat. u. Physiol. **8**:1, 1891.
7. Kultschitsky, N.: Arch. f. mikr. Anat. **49**:7, 1897.
8. Schmidt, J. E.: Arch. f. mikr. Anat. **36**:12, 1905.
9. Oberndorfer, Siegfried: Ergebn. d. allg. Path. u. path. Anat. **13**:586, 1909.
10. Gosset, A., and Masson, P.: Presse méd. **22**:237, 1914.

PRIMARY GASTRIC LEIOMYOSARCOMA

REPORT OF TWO CASES

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Ewing [1] estimated that about 1 per cent of all gastric tumors are sarcoma. Edwards and Wright [2] expressed the belief that there are probably more cases of sarcoma of the stomach than the literature indicates; in an extensive review they were able to find reports of only thirty-eight cases of myosarcoma of the stomach. It is my purpose to put two cases on record and discuss them briefly.

REPORTS OF CASES

CASE 1.—A white married man, aged 39, first admitted to the hospital on Dec. 2, 1932, complained of pain in the epigastrium and weakness. Three years before he had diarrhea for about seven months, alternating with constipation and accompanied by gnawing epigastric pains from one to two hours after meals, which was relieved by food and alkalis. A week before admission the patient was seized with severe pain in the epigastrium which tended to radiate to the left hypochondrium and umbilical region. He felt marked weakness and dizziness but did not vomit. Examination disclosed only a marked epigastric tenderness where a hard mass was felt. There were marked secondary anemia, blood in the stool and normal gastric juice except for the presence of blood. Several transfusions were given, and the patient was discharged improved, with the diagnosis of gastric hemorrhage secondary to gastric ulcer or carcinoma. Two weeks later the patient was readmitted, complaining of dizzy spells, weakness and tarry stools. A smooth globular filling defect was found near the cardiac end of the stomach extending up from the greater curvature. The area of the defect did not show the normal rugae. There was one area about 1 cm. in diameter which continually remained filled with barium as though it were an ulcer. After the loops of the small intestine became filled with barium, a large "vacuole" about 8 or 9 cm. in diameter was found just below the greater curvature in close relationship to the gastric deformity. Exploratory laparotomy was made. Between the greater curvature of the stomach and the transverse colon and between the two layers of the omentum was a bluish mass, twice the size of the adult fist, apparently a hemangioma. The tumor was adherent to the greater curvature by an isthmus continuous with an intragastric mass half the size of the extragastric tumor. No metastases were seen,

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From the Department of Pathology, Isaac Kaufmann Foundation, Montefiore Hosptal.

1. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

2. Edwards, C. R., and Wright, R. B.: Am. J. Surg. **19**:442, 1933.

and a partial gastrectomy was performed. The patient was discharged three weeks later after an uneventful recovery, with the hemoglobin 64 per cent and the red blood cell count 3,780,000.

The specimen consisted of a partially resected stomach with an attached tumor. The tumor was divided into intragastric and extragastric parts separated by a short pedicle. The intragastric mass was oval, measured 5 by 4 by 3 cm., was covered with normal gastric mucosa except one ulcerated area measuring 10 mm. in diameter and 5 mm. in depth, had a sharp margin, and was free from fibrosis or induration; the base was necrotic. The extragastric part, almost spherical, measured 12 cm. in diameter, was bluish purple, soft and fluctuating, and was covered with peritoneum. When sectioned, the intragastric mass was well outlined and separated from the gastric mucosa; it was pinkish gray, soft and friable. The extragastric part collapsed after incision and consisted of multiple cystic cavities filled with hemorrhagic fluid and loose fragments of broken-down tissue.

Fig. 1.—The resected part of the stomach in case 1, showing the intragastric and extragastric masses and the ulcerated area in the mucous membrane.

Microscopically, the main bulk of the tumor was composed of interlacing bundles of smooth muscle cells, uniform in size and shape, with areas of whorl formation. Other parts revealed large granular cells, mostly undifferentiated short spindle-shaped, oval or round cells; the nuclei were massive and rich in chromatin. There were also single and multinucleated giant cells and a few mitotic figures. The stroma was poor in connective tissue; the blood vessels were ill-defined sinusoids; no definite layers of the vascular walls could be identified. The extragastric part showed cystic degeneration; the tumor cells were swollen and stained poorly. The gastric mucosa was normal, and there was no evidence of infiltration with tumor cells. The diagnosis was: leiomyosarcoma of the stomach (intramural and subserous, undergoing degeneration).

Case 2.—An adult white woman, aged 32, was admitted to the hospital on Dec. 4, 1934, complaining of fainting after having vomited a large amount of blood. On that day the patient awoke with a gnawing sensation in the epigastrium, which

persisted until the early evening and was accompanied by numerous diarrheic movements, with the feces abnormally dark in color. Shortly after dinner, she felt extremely dizzy and nauseated, began to vomit blood and fainted. The hematemesis was repeated twice before she could be brought to the hospital. For the past

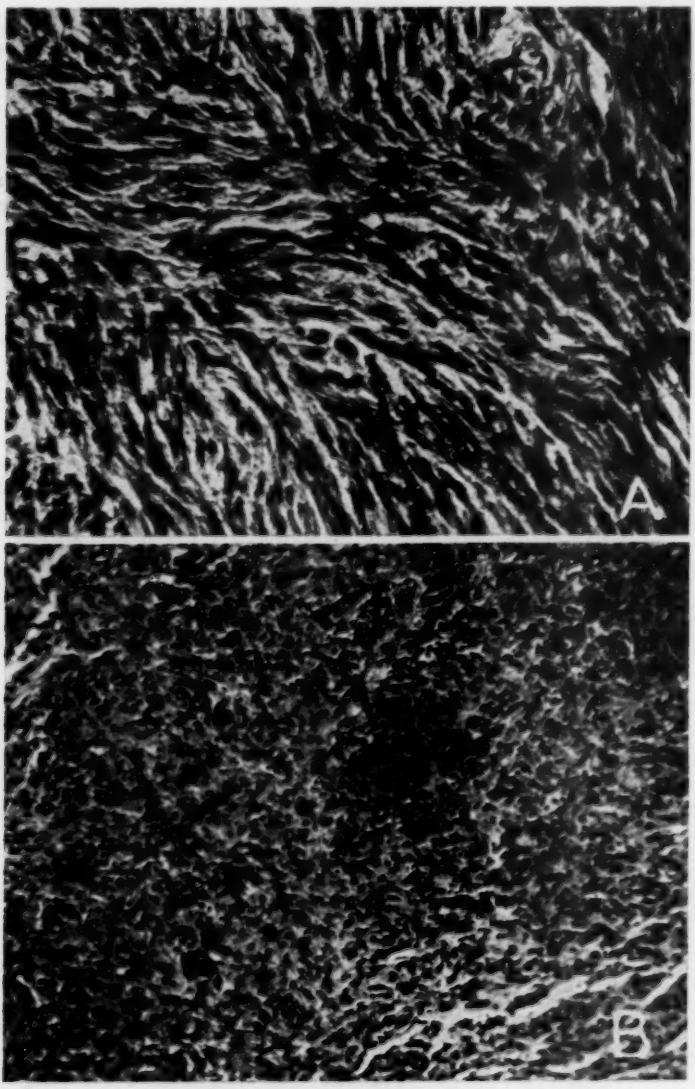

Fig. 2 (case 1).—*A*, smooth muscle cells in whorl formation; × 450. *B*, undifferentiated polymorphous cells; × 150.

nine years, the patient had had numerous gastro-intestinal complaints suggestive of disease of the gallbladder, a diagnosis which had been corroborated by a cholecystogram. Physical examination revealed only the appearance of shock, anemia

and obesity. No abdominal rigidity, tenderness or masses were apparent. The impression was that of gastric ulcer with hemorrhage and chronic cholecystitis and cholelithiasis.

The patient responded quickly to the usual treatment for shock. On the next day she received a transfusion of 500 cc. of citrated blood, and during the next week there was steady improvement on a modified Sippy diet with appropriate alkalis. At this time a large filling defect on the lesser curvature of the stomach close to the junction of the pars media and the pars cardia was reported. This was

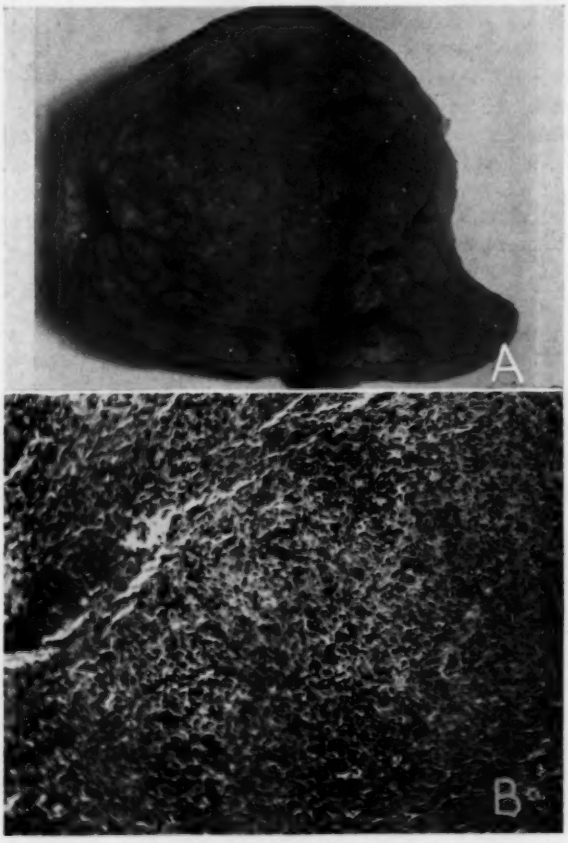

Fig. 3 (case 2).—*A*, the tumor with ulcerations in the mucous membrane. *B*, atypical cells without definite arrangement; × 100.

considered to be a large polypoid tumor of the stomach. A second transfusion was given, and an exploratory laparotomy was made. A tumor about the size of a golf ball situated on the anterior surface of the stomach midway between the greater and lesser curvatures was excised. The tumor did not appear to be malignant grossly. The patient was discharged two weeks later after an uneventful recovery.

The specimen was an oval tumor measuring 5 by 3 by 2 cm.; most of the surface was covered with gastric mucosa, and a small area with peritoneum. There were

three ulcers through the mucosa, the largest being 5 mm. in diameter and 4 mm. in depth. At the base of one of the ulcers there was a vessel with an eroded wall. The rugae were well preserved and apparently free from infiltration. The tumor was encapsulated; the main part was intragastric, and the smaller part protruded under the peritoneal covering. The cross-section revealed a pinkish-gray, fleshy, homogeneous mass, soft and friable.

Microscopic sections revealed a cellular and vascular structure. Most of the cells were smooth muscle cells, long spindle-shaped, with oval nuclei. The cells ran in bundles in all directions. They were well differentiated and had the characteristic appearance of the cells of benign myoma. Other areas showed cells that were poorly differentiated and variable in size and shape. The cytoplasm was granular; the nuclei were large and hyperchromatic, with one or two large, deeply stained nucleoli. There were a few giant cells and occasionally mitosis. The stroma had little connective tissue, but the capillaries and blood spaces were abundant, dilated and filled with red cells. There was slight lymphocytic infiltration throughout the stroma. The gastric mucosa was normal and separated from the tumor by normal muscularis mucosae. The diagnosis was: leiomyoma of the stomach (with sarcomatous changes).

COMMENT

The most common locations of gastric leiomyosarcoma are the curvatures of the stomach; it seldom involves the pyloric portion, and obstruction is therefore uncommon. The cardiac portion of the stomach was involved in none of the reported cases. The tumor varies in size from a minute growth a few millimeters in diameter to one so enormous that the entire abdominal cavity is filled. It is usually single, but occasionally multiple.

Anschutz and Konjetzny [3] divided sarcoma of the stomach into three classes from the gross point of view: intragastric, extragastric and infiltrating. It has been noted that leiomyosarcoma has a tendency to form intragastric or extragastric masses with pedicle formation, while lymphosarcoma generally infiltrates through the layers of the stomach. The cases now reported followed the general rule for the myosarcoma in their location. This type of tumor is well encapsulated and demarcated from the rest of the gastric layers, giving the appearance of an innocent tumor. Ulcerations through the mucosa are seen in many cases, as in these two cases, the first having a single ulcer and the second multiple ulcers eroding the big vessels of the submucosa with subsequent massive hemorrhage. Furthermore, the tumor has a tendency to softening with formation of cysts. Metastasis has been observed in a few cases. It is generally limited to the abdominal organs. The metastasizing cells may spread by invasion of contiguous tissues, by implantation on the omentum and various parts of the intestines and

3. Anschutz, W., and Konjetzny, G. E.: Die Geschwülste der Magens, Stuttgart, Ferdinand Enke, 1921.

by carriage to the liver and distant organs. Kaufmann [4] stated that the extragastric and submucosal varieties are of long duration and not of a high grade of malignancy. He believed that metastases occur in only one third of cases in which there is no operation, and that the most frequent site is the abdominal lymph nodes. The first patient, at the time of writing, two years and four months after operation, is free from symptoms of recurrence, and roentgen examination of the stomach and lungs shows no signs of it. In the second case only a few months have elapsed since the operation.

The determination of the origin of the tumor depends on the type of cells forming the main bulk. At times this is fairly simple and definite, while at others, because of marked anaplasia of the cells, it is doubtful. In both cases, as the photomicrographs show, there are areas that have the appearance of cellular myoma, while other parts show undifferentiated cells with hyperchromatic nuclei. This cellular myomatous appearance in many areas of the tumor has been the cause of controversy as to malignancy: Some authors hold that such tumors are benign and that no recurrence should be expected after extirpation, while others report cases of benign myomatous growths that have taken on malignant properties.

SUMMARY

Two cases of primary leiomyosarcoma of the stomach are reported. There were areas resembling benign myoma and also sarcomatous areas. Since primary leiomyosarcoma of the stomach still is a rarity in comparison with other neoplasms of the stomach, and as most of the cases on record are reports of observations at necropsy, cases diagnosed before death should be placed on record. The incidence of gastric sarcoma is in the ratio of from 1 : 100 to 1 : 300 of all gastric tumors. Myosarcoma tends to grow intragastrically and extragastrically and to undergo cystic degeneration and ulcerations; therefore hematemesis or melena is common. The consensus is that the type of tumor just reported has little tendency to metastasize and hence is the least malignant of the malignant neoplasms of the stomach.

4. Kaufmann, Edward: Pathology for Students and Practitioners, Philadelphia, P. Blakiston's Son & Co., 1929, vol. 1, p. 692.

General Review

PATHOLOGY OF YAWS

ESPECIALLY THE RELATION OF YAWS TO SYPHILIS

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When one is endeavoring to trace the origin of syphilis, the relation of syphilis to yaws arises as a problem connected with, perhaps inseparable from, the original problem. In both infections there are a primary lesion and an ensuing state of generalized lesions; spirochetes of similar form occur in the early lesions of the two diseases, and in both the serum reactions (Wassermann, Kahn) become positive and the lesions usually clear up when arsphenamine and similar preparations are used. There are also differences between syphilis and yaws. My purpose in this paper is to discuss the resemblances and differences, particularly from the point of view of the structural changes. Comparisons of yaws with syphilis have been made many times, but the changes in structure have usually been given less attention than the other aspects of the problem. The history of yaws will not be considered here; it may possibly be taken up in a later paper.

As yaws does not occur in the United States, many pathologists may not be as familiar with it as they are with syphilis. I shall therefore give certain facts concerning yaws as they appear in the literature, attempting at the same time to note points in which yaws and syphilis are alike or different. Attention will be called to references that give reviews of the extensive bibliography.

INCIDENCE, TRANSMISSION AND SYMPTOMS

Yaws is also known as frambesia (on most of the continent of Europe), pian (in France and the West Indies) and bubas (in many Spanish American countries) and by other local names. It occurs almost exclusively in the tropics or in regions closely adjacent to the tropics. Prominent localities for it are Haiti and Jamaica and other islands of the West Indies; some parts of Central America and of tropical South America (chiefly Brazil and the north coast); various Polynesian and Melanesian islands, such as Fiji and Samoa and the Solomon Islands; Australia; New Guinea; Guam; the Philippine Islands; Netherlands Indies and notably Java and Sumatra; French Indo-China; the Federated Malay States; Ceylon; a few parts of British

India (chiefly Burma and Assam); Madagascar, and an immense territory in tropical Africa. Its absence among the Negroes of the southern parts of the United States is noteworthy (see extensive bibliography and history given by Wood).

Yaws is sometimes curiously uneven in its distribution, being present in a given locality and absent from neighboring localities for no apparent reason. The disease is occasionally imported into a country with a temperate climate through a seaport, such as New York, but the infection does not spread among the general population. Powell described graphically the dissemination of yaws through Assam from a single small focus of infection. Yaws is said to occur less frequently in towns than in rural districts, and that may be partly the result of treatment or of voluntary or enforced segregation of patients. At high altitudes in the tropics the lesions of yaws are likely to appear in warm, moist parts of the surface of the body (Lopez-Rizal and Sellards). It usually occurs in members of dark-skinned races. While cases in white persons have been described, they are rare. Yaws affects persons of the poorer classes more often than the well-to-do.

Children and young adults are most likely to show the early manifestations of yaws. Frequently several members of a family are affected at one time. By nursing at the breast an infant may be infected by the mother, or the nursing infant may infect the mother. Sexual transmission may occur but is rare. The ordinary mode of transmission is evidently contact with fresh lesions, often at points where there has been slight injury or a preexisting ulcer. The scanty clothing of the natives of tropical countries, the naked children, the bare feet and the little huts or cabins where many people are huddled together give plenty of chances for contact. It is common to see the sores of a native with yaws crawling with ants or flies, which the sufferer seems not to notice, and doubtless the infection is often spread in that way. In certain localities biting flies probably inoculate the victims. Spirochetes have been found on or in flies and mosquitoes that have been in contact with the ulcers of yaws (Baermann, Krum, Turner and Peat). Yaws has been known to follow vaccination with cowpox (Powell, Wilson). As with syphilis, the point of primary invasion may be overlooked or forgotten, or possibly there may not be any visible primary lesion (Sellards and his associates, 1926). If hereditary or congenital yaws occurs, it must be rare. Most observers have denied that it exists, though Butler (1930) expressed the belief that it does occur. Léon's careful researches seem to leave the question unsettled.

Yaws, like syphilis, may be divided for convenience into primary, secondary and tertiary stages, but the stages do not seem to be as well defined as those of syphilis. The incubation period is said to be about three weeks, but it may be shorter or considerably longer. In the early

stages of yaws there may be the general symptoms that are noted in most cases of acute infection of moderate degree, such as lassitude, pains in the bones and joints, sometimes fairly severe, and a slight rise of temperature. Often no constitutional disturbance is mentioned. Serum reactions, such as the Wassermann and Kahn reactions, become positive.

SPIROCHETES

Shortly after Spirochaeta pallida was discovered, Castellani observed a similar organism in the serum of the papillomas of patients with yaws. The nomenclature of the group of spirochetes is still in a state of confusion. The name Treponema pertenue is employed for the organism of yaws by most writers of recent date and seems to have been adopted by Castellani. As will be seen farther on, there are many cases in which it is difficult to determine whether one is dealing with yaws or with syphilis, some writers using the word treponematosis to designate those doubtful cases.

Spirochaeta pertenuis, Spirochaeta pallidula or T. pertenue is similar to S. pallida morphologically, being well described and illustrated by Ashburn and Craig. A few observers have stated that differences in form or staining properties exist, but there now seems to be fairly general agreement that there are no constant differences. The spirochete may be found in papillomas of the first and second stages without difficulty in most instances. Dark-field illumination and various staining methods may be used as for S. pallida. Cultures have been secured in the same manner as for S. pallida but with great difficulty; not much seems to have been done in that direction. As it is doubtful that the spirochetes cultivated from patients with syphilis are the ones that produce that disease, a similar doubt must prevail for the spirochetes cultivated from the patients with yaws. Hallenberger said that he secured cultures easily in horse serum and successfully inoculated two Negroes with the cultures.

PRIMARY STAGE

The initial lesion is known as the "mother yaw," *maman pian* and *madre buba* and by similar names in different countries. In Haiti it occurs on the foot or on the leg below the knee in a majority of cases (Wilson and Mathis), though it may arise on any exposed part, such as the lip, face, breast or hand. The lesion appears as a papule which enlarges and becomes moist, and the discharge and the cells may dry on the surface, forming a crust. The lesion may lose part of its epithelial covering and form an ulcer. It is said not to be indurated (Rat and many others). However, Butler (1935) called attention to the fact that syphilitic chancres often lack induration or any distinctive gross characteristic. Extragenital chancres especially may lack characteristic

hardness (Hutchinson). The ulcer may be from 1 to 2 cm. in diameter or larger. It may heal promptly, may persist into the secondary stage

Fig. 1.—Probable primary lesion of yaws on the right thumb of a Negro woman aged about 38, of Leogane, Haiti. It was stated that "the lesion appeared one and one-half months before, after an eruption which occurred during washing. There was no other eruption on the body." (Gatherings of women to wash clothes at a well or pond are important social functions in Haiti.) The Haitian physicians made a diagnosis of yaws.

Fig. 2.—Cross-section of tissue removed at biopsy from the lesion shown in figure 1. When stained by the Levaditi method it showed a small number of typical spirochetes among the disorganized epithelial cells, rather deep down. Small numbers of gram-positive cocci were found among the deep epithelial cells. The tissue was given to me by Dr. Joseph Perrier, Port au Prince.

or, according to some observers, unlike the chancre of syphilis may still be present in the form of a chronic ulcer in the tertiary stage (Wilson

and Mathis). The diagnosis of a primary lesion without other manifestations of yaws must be somewhat uncertain (figs. 1 and 3).

Histologic Aspect.—The histologic aspect seems not to have been studied in as many cases as that of the secondary papilloma of yaws.

Fig. 3.—A woman aged about 20 who came to the Haitian General Hospital, Port au Prince, from a small village. The *maman pian,* shown at the right, was on the inner side of the right leg, 7 cm. above the malleolus and measured 4 by 3 cm. It was said to have been present for three months. It was slightly elevated and reddish, with some yellow crusts, and had the appearance of a chronic granulating ulcer. Some pale, flat macules were present on the upper part of each arm and on the chest, said to be the remains of an earlier eruption that had disappeared spontaneously. The main lesions had rounded borders; they were from 1 to 2 cm. or more in diameter, elevated and covered with grayish-white crusts. They occurred on the thighs and trunk and especially on the face. The reticular appearance of the dried exudate on some of the papules on the face is unusual, I believe (possibly due to treatment). The skin close to the papules was usually a little more deeply pigmented than the general surface. It was said that in films from the primary lesion, stained by Fontana's method, a few spirochetes were demonstrated with great difficulty, probably owing to the fact that the patient had an injection of arsphenamine five days before. The woman complained of pain, limped and appeared languid. There was a trifling rise of temperature. Eighteen days later, the treatment having been continued, the eruption had entirely disappeared, leaving mostly pale areas, but sometimes an increase of pigment. The patient appeared to be well. The primary lesion was greatly reduced in size. Like many of the illustrations shown in textbooks and articles, the picture represents an extreme and not an average case. These photographs were taken by Mevs, Port au Prince, Haiti.

A few observers (Hallenberger; Stitt, 1929) have stated that primary and secondary lesions have a similar structure. As the chancre of syphilis has perhaps a more characteristic histologic picture than any other lesion of syphilis, it is unfortunate that there are so few studies on the primary lesions of yaws for comparison. To be convincing a primary lesion from a patient in whom typical secondary papules of yaws were already present or developed later would be desirable; also a comparison with extragenital syphilitic chancres would be important. I have studied sections from a probable primary lesion of yaws, but no secondary eruption was mentioned at the time the biopsy was made, and the patient was not seen again. The structure (fig. 2) was the same as that of the secondary papules of yaws that I have seen: infiltration of the epithelium with polymorphonuclear leukocytes;[1] marked acanthosis; infiltration of the papillae and underlying connective tissue with lymphocytes, plasma cells and leukocytes; slight infiltration around the blood vessels, and doubtful slight multiplication of the endothelium of the small blood vessels. The changes in and around the blood vessels were distinctly less marked than those in sections of genital chancres available to me for study. Typical spirochetes were observed in sections stained by the Levaditi method; they were not numerous and were in regions where the epithelium was split up by the infiltrating cells.

SECONDARY STAGE

The secondary stage is usually regarded as presenting chiefly superficial lesions of the skin. As it is not characterized by any symptoms indicating specific involvement of the viscera, it is assumed that the viscera are not involved. I have not seen an account of an autopsy in a case of acute florid yaws. An opportunity for such an autopsy would be offered only in a case of most unusual severity (Baermann) or more probably in a case in which death occurred through violence or from some intercurrent disease. Reports on animals inoculated successfully with yaws on which autopsies have been made have not mentioned any important changes in the viscera.

The characteristic eruption of yaws is said to begin from two to eight weeks, or even considerably longer, after the appearance of the primary lesion. Allowing for odd and unusual cases, which will be referred to later, which occur in all diseases, and for those in which no secondary lesions are manifested, the eruption follows a pattern that is often described as "monotonous" in its regularity. Practically all observers agree that it is the one certain diagnostic feature of the disease. This monotonous eruption is different from syphilitic eruptions

1. In the remainder of this article, for the sake of brevity, I shall call polymorphonuclear leukocytes simply leukocytes.

(Fox, 1929) except those syphilids that are called frambesiform, some instances of rupial syphilis and some condylomas, which are like the papules of yaws seen on moist parts of the skin.

In his article on syphilis in the tropics Manteufel stated that secondary papular syphilids in the tropics may sometimes resemble the secondary eruption of yaws and that, on the other hand, the secondary

Fig. 4.—Lesions on the flexor aspect of the legs of a 13 year old girl with an extensive general eruption and a strongly positive Wassermann reaction. Two younger brothers were similarly affected. This photograph was given to me by Dr. C. M. Hasselmann, Manila.

eruption of yaws may at times resemble secondary syphilids (see also the article by Schüffner).

The eruption of yaws begins in the form of papules, which enlarge, often to the diameter of a centimeter or considerably more, and appear as moist papillomas. Several papules may become confluent. Exudate,

dead epithelium and leukocytes coat the surface with a yellowish or dirty white covering. When that layer is peeled off there remains a reddish granular mass, said to look like a raspberry (hence the name frambesia from the French word for raspberry). The name polypapillomas is descriptive but is not often used (figs. 3 to 5). These yaws are generally multiple, often widely distributed, rarely occurring on mucous membranes but frequent at mucocutaneous junctions.

Fig. 5.—A family of Madioen, Java, before and after treatment for yaws. The photographs were given to me by the Public Health Service of Netherlands Indies through Dr. John L. Hydrick, of the Rockefeller Foundation.

Schöbl (1928, p. 218) failed in his attempts to infect the nasal or vaginal mucous membrane of monkeys. The scalp is rarely involved. Paronychia occurs but is not common. The characteristic eruption may be preceded by a roseola (Schüffner) or by a fine desquamation at various points. Some observers have emphasized itching as a symptom (Rat, Manson-Bahr, Castellani and Chalmers, Jeanselme). Some have stated

that of a large number of papules produced metastatically, only a small part develop so as to become typical of secondary yaws (Rat, Sellards). Most writers seem to have held the opinion that the organisms causing the disease are distributed from the primary lesion by way of the blood stream. New points of infection apparently may arise also from the rubbing of an infected surface against an adjacent surface, as from one thigh to the other (Wilson). It is beyond the scope of this article to describe unusual departures from typical yaws, but annular or circinate lesions may be mentioned because of their comparative frequency (fig. 6).

The papillomas of yaws may heal spontaneously, or they may persist for a long time (from two to six months or more, Schüffner). In healing they leave areas that are sometimes lighter and sometimes darker

Fig. 6.—A circinate form of yaws, so-called ringworm yaws, on a Negro girl aged about 6 years. The mother yaw appeared on the foot three months before, and the secondary yaws, a month later, according to the history. There were a few lesions about the vúlva. No treatment had been given as yet. The clinical diagnosis of yaws was made by experienced physicians at Leogane, Haiti.

than the adjacent skin (Baermann). Under treatment with modern arsenical preparations (introduced for the treatment of yaws by Strong in 1910) the lesions disappear in a fashion that observers characterize as magical, dramatic or miraculous. Data are lacking that show whether or not these apparent cures are permanent, but the results may be called encouraging (Sellards, 1923; Lopez-Rizal and his associates, 1926; Moss; Baermann; Butler [1930]; Lambert). In several localities a reduction in the prevalence of yaws following the treatment of large numbers of patients has been reported (Turner, Saunders and Johnston).

Lymphatic Glands.—Most writers on yaws have given little space to the subject of the lymphatic glands. Rat referred to the enlarge-

ments that he saw as sympathetic and unimportant. Nevertheless enlargement of the regional glands has been mentioned by many as being common. The inguinal and epitrochlear glands have been referred to as being involved frequently, but other regions also may be affected.

Sellards, Lacy and Schöbl observed that the regional lymphatic glands enlarged in from six to seven weeks after experimental inoculations in 6 human subjects. Harley found the epitrochlear glands palpable in 79.1 per cent of more than 5,000 cases of late yaws. Usually it has been stated that enlargement of the lymph nodes is slight, but in certain localities Lopez-Rizal and Sellards found enormous enlargement. It has been suggested that involvement of the lymphatic glands may be due in part to secondary infection (Moss and Bigelow, Wilson). In sections of an epitrochlear gland White and Tyzzer did not observe any marked change except hyperemia. The spirochetes have been demonstrated in the lymphatic glands in cases of active yaws (Ikegami; White and Tyzzer; Baermann; Schöbl, in monkeys, 1928).

Lesions of Bones.—Lesions of the bones have been described as occurring in the secondary stage. They will be discussed in connection with the tertiary stage.

Histologic Aspect of Secondary Yaws.—All the descriptions that I have seen have apparently been founded on sections of lesions of the skin removed at biopsy (figs. 7 to 9). The condition is usually characterized as a granuloma, with much proliferation of the epidermis and much emigration of leukocytes.

The outer layer of epidermis is thickened and of a hyaline appearance and is coated with dried serum and cells. The deeper, interpapillary part proliferates downward; the acanthosis is usually marked. The pigment may be diminished in amount or wholly lacking in the epithelium of the area affected (Kellermann Deibel and Elsbach, Hallenberger). Mitotic figures may be seen in the epithelial cells in material that has been well fixed and stained.

The corium is infiltrated with numerous cells: lymphocytes, plasma cells, spindle-shaped cells, large mononuclears and leukocytes. The descriptions do not lay much stress on the edema, the dilatation of blood vessels and the small hemorrhages that are sometimes seen; injury inflicted by removal of material for biopsy may be responsible for these results in part. Many observers have stated that the infiltration consists chiefly of plasma cells, especially in older lesions, and some even apply the name plasmoma to the condition. Others have not observed that plasma cells are especially conspicuous, and that has been my own experience. While there may be some perivascular arrangement of cells in the corium, the tendency of the cells to gather about the vessels is

not marked. Endarteritis and periarteritis are not more noticeable than in many inflammatory areas, in contrast to what is common in syphilis. Giant cells are rarely seen. In some cases eosinophils are numerous in

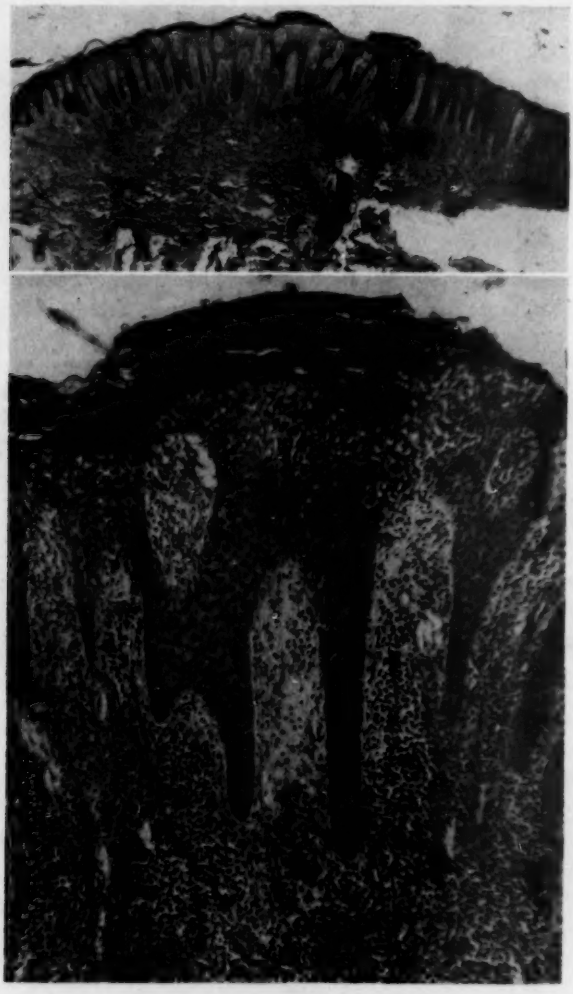

Fig. 7.—Cross-sections of one of the early papules on the back of a 10 year old Filipino girl before treatment was begun. I saw this patient with Dr. Chiuto at the San Lazaro Hospital, Manila. She had had secondary lesions for about three weeks, a moderate number on the back and a few other scattered lesions. The photographs were made from sections prepared by Dr. Manalang, pathologist to the hospital. Pigment was diminished in amount or was absent beyond the normal edge. Leukocytes could be seen emigrating through the epidermis, though there were no actual abscesses. The cells in the corium were lymphocytes and plasma cells, with some leukocytes next to the epithelium. The blood vessels were not notably involved.

the corium. As patients in the tropics are so often infested with intestinal and other worms, that fact might be noted in connection with the eosinophilia. Some form of allergic reaction might also be considered. Mast cells have been mentioned by some observers, but they do not seem to be important. New capillaries have rarely been mentioned.

Leukocytes are usually found invading the epidermis in large numbers; they may obscure the junction of the epidermis and corium, and they may be seen in all the layers of the epidermis in the process of migration. In some of my sections epithelial cells and exudate made a small homogeneous necrotic area, and when invaded by leukocytes this matrix looked curiously like cartilage or osteoid tissue (Gram-Weigert

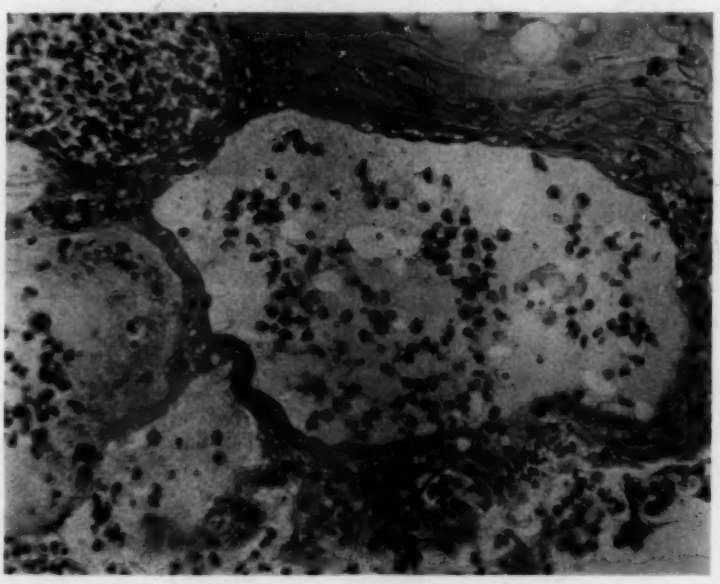

Fig. 8.—Section of a secondary lesion of yaws given me by Prof. Gomez and Dr. Santa Cruz, of the Philippine Bureau of Science, Manila, showing abscesses in the epidermis. In the deeper parts, not included in the figure, downward growths of epithelium, with considerable numbers of mitoses, were seen. The corium contained collections of lymphocytes and plasma cells, numerous eosinophils and many leukocytes next to the epithelium. The blood vessels were not notably involved.

stain); apparently new capillaries also invaded the mass. Small abscesses may form on the surfaces of the papillae, just below the epidermis; or abscesses may be observed in the layers of the epidermis when its cells become separated, forming cavities that are filled with leukocytes (fig. 8). These abscesses may contain many spirochetes (fig. 9). The spirochetes of yaws are said to be epidermotrophic, because most observers have found them chiefly in the epidermis

(Schüffner and many others). They are readily demonstrated by the Levaditi method in sections. In nine of the eleven secondary papillomas of yaws that I prepared by the Levaditi method, characteristic spirochetes were shown and occurred almost exclusively in the epidermis. Among collections of spirochetes one may see granules the appearance of which suggests an origin from disintegrated organisms. The neighboring cells may show evidences of degeneration or disintegration. It is difficult to say whether or not the organisms occur within cells.

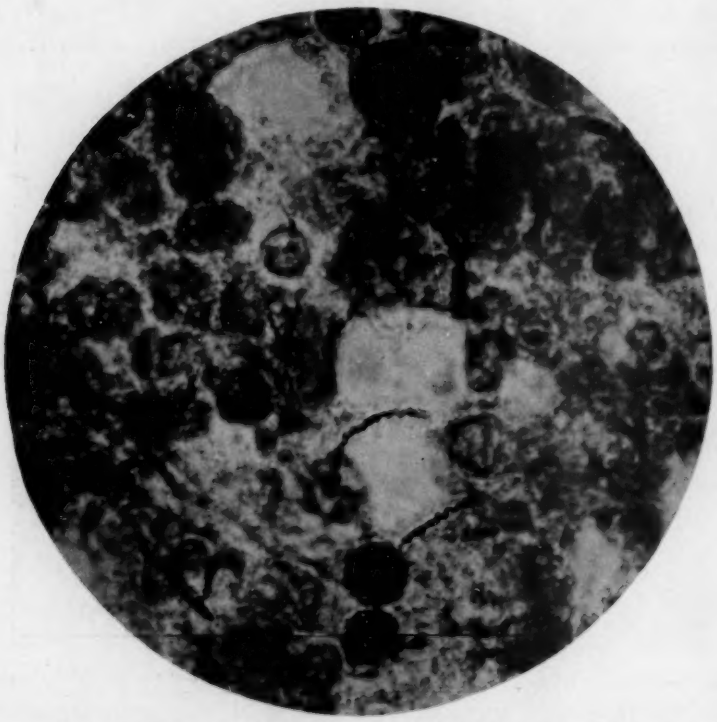

Fig. 9.—Enlargement of a portion of a section from the lesion shown in figure 8 but stained by the Levaditi method. Part of one of the abscesses in the epidermis with numerous spirochetes is shown. It would be interesting to have similar abscesses examined also for pyogenic cocci by Gram's method.

In sections from a patient with an early stage of yaws, Goodpasture demonstrated spirochetes in large numbers in the perivascular tissue in the terminal portions of some papillae. He expressed the belief that the organisms were brought by the blood stream, and that the lesion began at that point and spread from there to the epidermis. Goodpasture also found that in sections of papillomas of yaws excised forty hours after the injection of neoarsphenamine and prepared by the Levaditi method no spirochetes could be demonstrated. He stated that

there was a great deal of destruction of leukocytes and much phagocytosis of leukocytes by large mononuclear cells in the same sections.

In sections made in several recent cases and stained by the Gram-Weigert method I have seen good-sized colonies of gram-positive cocci and less often other organisms, usually just below the partly necrotic epidermis. It can hardly be doubted that secondary infection plays an important part in many cases of yaws, but evidence is lacking to show how much the microscopic picture is modified by secondary infection.

Summary of Histologic Aspects of Secondary Yaws.—The conception of the secondary papules of yaws that is derived from the work of various students is that the spirochetes usually reach the papillae of the skin by way of the blood stream from the primary focus or the regional lymphatic glands; probably in some cases direct inoculation from a neighboring part also takes place. By whatever route the organisms reach the starting point of the secondary growth, their multiplication proceeds chiefly in the epidermis. Downgrowth of the epidermis and migration of leukocytes into it are the outstanding features. At the same time new cells appear in the corium; practically all possible types of cells found in inflammatory areas are present except giant cells, which are rarely observed. The name plasmoma or even granuloma is somewhat misleading as it fails to suggest the significant involvement of the epidermis. The growth of the organism, chiefly in the epidermis, and the absence of marked involvement of the blood vessels are the most striking of the differences in the histologic picture of secondary lesions in yaws from those of syphilis. Syphilitic condyloma in particular, but also rupia and frambesiform syphilids, may give pictures that closely resemble those seen in yaws. But, on the whole, investigators seem to have agreed that if a number of cases are compared, more involvement of blood vessels will be observed even in these forms of syphilis than in the secondary papillomas of yaws. This is an exceedingly conservative statement.

Histologic reports have been given by Fox, Hallenberger, Jeanselme, Kellermann Deibel and Elsbach, MacLeod, Marshall, Schamberg and Klauder, Stitt (1929), Strong and Shattuck (1930) and White and Tyzzer. In their articles some additional references are given.

Crab Yaws and Clavus.—Crab yaws and clavus, or clavos, are names given to certain lesions of the soles of the feet, crab yaws referring to the gait, which is thought to resemble the motion of a crab. Clavos is derived from the Spanish word for nails. There appear to be two conditions included under these names: (1) nodular lesions beneath the thick epidermis of the soles of the feet, which may break through to the surface, leaving ulcers or holes (Moss and Bigelow), and (2) hyperkeratosis of the epidermis, with cracks and fissures (fig. 10).

Many writers place these conditions, especially the nodular form, in the late secondary stage of yaws. To what extent the two conditions coincide is not clear from the literature (Schöbl, 1928). The practice of going barefoot may have some influence on the hyperkeratosis. The palms of the hands may be involved in similar processes, but more rarely. If the lesions are of sufficiently early origin to contain living spirochetes, the serum exuding from them may offer one more means for spreading the infection. At rural dispensaries it is common to see several barefoot patients with lesions of the soles of the feet standing about the premises. At the station of the Rockefeller Foundation, Kingston, Jamaica, Dr. T. B. Turner told me that he has found

Fig. 10.—Crab yaws on a patient at Kenskoff, Haiti (altitude of about 4,000 feet). Some of the white spots were pebbles lodged in the cracks in the epidermis. The clinical diagnosis was made by Haitian physicians.

motile spirochetes fairly regularly by dark-field illumination in the serum from the lesions of crab yaws. The histologic picture of the hyperkeratosis has been described by Gutierrez (1923). It has been said that inoculated monkeys sometimes show keratoderma closely resembling that seen in yaws in human beings (Schöbl and Hasselmann).

TERTIARY STAGE

Disease of Bone in Yaws.—For many years it has been alleged that the bones may be affected in late yaws, and a large number of observers in practically all parts of the tropics have alluded to this condition.

Some have denied that bone lesions are produced by yaws, and some still express doubt in this regard. Nodules resembling gummas, dactylitis, thickening of the bone proceeding from the periosteum and a sabre-shaped tibia are among the forms described. When thickening takes place beneath a chronic ulcer, it could be the result of a secondary periostitis and not directly due to yaws. The bone disease thus far described is not distinguishable grossly from that seen in cases of late syphilis. The argument advanced is that the disease of bone occurs in persons giving a history of having had yaws and showing the scars of previous yaws and that yaws is common in the district and syphilis rare or unknown.

Since the introduction of the roentgen rays more accurate studies are possible. It now appears that changes in the bones, which may be accompanied with considerable pain, may take place while papillomas of unmistakable active yaws are still present. Schüffner, in his report of cases in Netherlands Indies, was among the first to publish roentgenograms of the bones. The changes shown in his excellent roentgenograms could not be distinguished from syphilitic osteoperiostitis, while his diagnosis of yaws (in one instance of acute florid yaws) was of course conclusive. Soetomo and Eichorn, and Polak gave illustrations of other cases from Java. Maul described a series of patients seen in the Philippines and gave roentgenograms. In one case he published excellent photographs showing the primary lesion and unmistakable secondary papillomas and roentgenograms from the same subject. Maul's results differed from those of Schüffner in showing most commonly areas of rarefaction in the interior of bones, occasionally reaching the surface of the joint. In most cases there was one or a few of these areas, but one subject presented one hundred and thirteen. Several other processes, such as abscess, could produce similar pictures. Maul has found only a small percentage of cases of swelling of the surface or periosteal thickening.

At Kingston, Jamaica, in 1933 Drs. Turner and Saunders, of the Yaws Commission of the Rockefeller Foundation, showed me a large number of roentgenograms of children (fig. 11). Some of the children were said to have shown active lesions of the skin; in some, spirochetes were demonstrated in the lesions of the skin; others gave a history of having had yaws. According to my notes, the changes appeared in long bones and were of three types: areas of absorption, areas of absorption surrounded apparently by a region where there was new formation of bone and thickening of bones proceeding from the periosteum. The two latter types could not be distinguished from the changes produced by syphilis. The first type, simply showing areas of absorption, was the most frequent; the areas were from 0.5 to 2 cm. in diameter. Their

results will be published later, but I have been permitted to make this statement in advance.

At Batavia, Java, Dr. van der Plaats showed me roentgenograms of 7 patients for whom a clinical diagnosis of frambesia had already been made by other physicians. According to my notes, the films showed thickening of bone from osteoperiostitis like that of syphilis, areas like

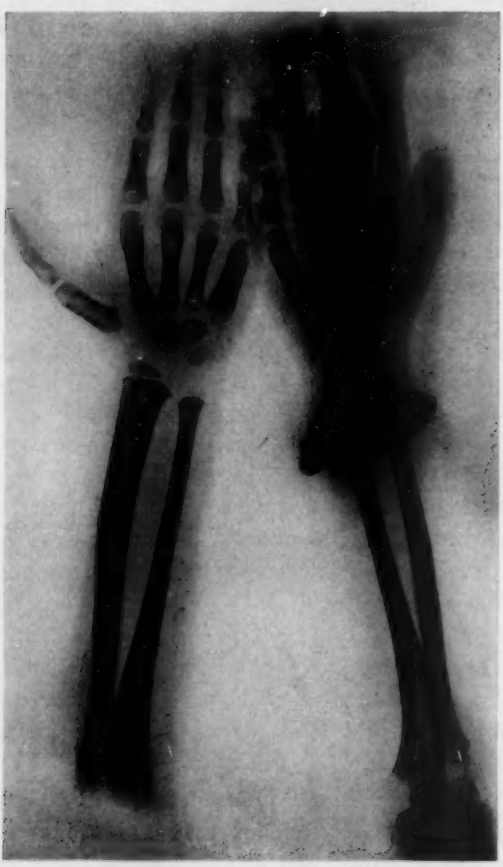

Fig. 11.—Roentgenogram of the hands and forearms of a 6 year old girl who had acquired yaws two years previously. She was given injections at that time, but osseous lesions and ulcerative cutaneous lesions developed a year later and persisted. This roentgenogram was made at the Kingston (Jamaica) Hospital and given to me by Dr. T. B. Turner, of the Rockefeller Foundation. No secondary frambesiform lesions of the skin were then present, but Dr. Turner had no doubt as to the diagnosis.

those produced by syphilitic gummas, and areas that might have been the result of osteomyelitis. Iseki reported a case of early yaws in which frambesic papules and disease of the bones were present at the

same time. Professor Ver Bunt, of Batavia, recently informed me that after reviewing the cases of patients with frambesia showing bone lesions who had come to his clinic during the preceding year, rather to his surprise it appeared that no patient showed osseous lesions simultaneously with the papulocrustate eruption; that is, the osseous lesions in this series were late lesions. Montel and Couput also described late lesions.

In general, observers seem to have agreed that the acute lesions of yaws in bones are commonest in children and that the bones of the hands, feet, legs and arms are most often involved. From what has been said it appears that some of the changes seen in roentgenograms are indistinguishable from those resulting from syphilis. However, the curious areas of absorption of bone, often multiple, are unlike the changes usually described for syphilis. They perhaps resemble some of the areas described by McLean in congenital syphilis of bone in young children. Direct action of the spirochetes, their toxins, allergy, secondary infection and mixed infection are among the possible explanations for the changes in the bones that suggest themselves. Histologic study of the bones in a series of these cases might furnish a solution.

Wolter gave a brief histologic description of a lesion in a case of dactylitis, apparently in a child (taken from Hashiguchi, whose work is not now accessible to me). There were thickening of the periosteum, with edema, slight infiltration of lymphocytes, plasma cells and fibroblasts; leukocytes were occasionally seen, especially in and about the walls of small veins with a more or less swollen endothelium. Proliferation of the capillaries, the smallest veins and the lymph clefts was observed. Necrosis and scarring were not demonstrated. Spirochetes were not seen. Wolter expressed the opinion that the dactylitis was similar to that of congenital syphilis but that it must be very rare in frambesia. He suggested allergy as an explanation. I do not know of any other histologic studies of the bones in yaws. Hermans described arthritis and involvement of tendons among the late results of yaws.

One point of difference from syphilis may be mentioned here. The involvement of the outer surface of the skull, especially the frontal and parietal bones, in a gummatous periostitis has long been regarded as frequent in severe cases of tertiary syphilis, but it is rarely seen today. The worm-eaten appearance of such a skull is well known. There is practically no evidence that yaws produces this type of skull. Sir Arthur Keith informed me of a skull of that type from the Society Islands, said to be that of a patient with yaws, but without other proof. Georg described a doubtful case from the Dominican Republic, which was probably a case of syphilis. In the literature I have not seen any report of the production of lesions of the bones in animals that had been inoculated successfully with the virus of yaws (with the excep-

tion of that of Hashiguchi quoted by Matsumoto). That includes the extensive series of monkeys infected by Schöbl and the rabbits described in a recent report by Turner and Chesney. Bone marrow from infected monkeys inoculated into other monkeys is said to have produced yaws (Neisser and his associates, quoted by Maul). In animals infected with syphilis, however, disease of the bones has been recorded many times.

Late Ulcers.—The difficulty or impossibility of distinguishing some of the late manifestations of yaws from the late lesions of syphilis has long been recognized. In articles published in recent years there has been shown an increasing tendency to admit that certain lesions may be due to yaws that formerly would have been attributed to syphilis. Some writers have considered that certain mutilating forms of syphilis that are alleged to occur in the tropics are really yaws. The arguments for regarding these lesions as due to yaws are that in the communities in question primary venereal chancre and typical secondary cutaneous eruptions of syphilis are said to be rare, miscarriages among the women are rare and signs of congenital syphilis among the children are wanting, while yaws in the early stages is frequent.

Chronic ulcers that cannot be distinguished from the late ulcers of syphilis seem to occur frequently in late stages of yaws. Sometimes the ulcers arise from early lesions that have not healed; more often they appear first after an interval of months or years after the original attack. They often occur on the leg and may originate in the breaking down of nodules in the skin that are like gummas. The ulcers may heal after the destruction of a great deal of tissue and may lead to contractures and grave deformities. I have not encountered any reference in the literature to the development of epithelioma on the late ulcers of yaws, and that must be an uncommon occurrence; I have learned of a few instances in personal communications.

Dr. H. M. Wade, of Culion, Philippine Islands, has sent me several photographs of patients with chronic ulcerative conditions, sometimes resulting in a great deal of scarring and deformity. The lesions had been diagnosed incorrectly as leprosy and in Dr. Wade's opinion probably represented late stages of yaws. Specimens such as those illustrate forcibly the difficulties of diagnosis in many cases of chronic ulceration in tropical countries. The same difficulties are well illustrated in the reports of Strong and others on work in Brazil and in Liberia (1925, 1930).

Gangosa.—Gangosa and rhinopharyngitis mutilans are terms that are used more or less interchangeably. The word gangosa, first employed in the island of Guam, is derived from the Spanish word meaning nasal voice. In this disease there may be destruction of the soft parts of the nose and the adjacent parts of the face and of the palate. There may

also be destruction of bone. Shocking mutilation may result, the process sometimes even extending to and destroying the eye. Gangosa commonly resembles types of late syphilis that formerly were seen in Europe and the United States but that have become rare at the present time. In localities where both syphilis and yaws are prevalent it may be impossible to make a positive diagnosis. In some instances gangosa is also said to resemble lupus, leprosy, blastomycosis and leishmaniasis. In some places where yaws is prevalent there may be many cases of gangosa, and in others, very few (Rat). Hunt and Johnson, who studied 2,000 cases of yaws in Samoa, stated that gangosa was excessively rare,

Fig. 12.—Gangosa (rhinopharyngitis mutilans) in a man aged 24. The soft palate but not the hard palate was perforated. I saw the patient several months after the photograph was taken, and there had been great improvement. The diagnosis was made by Prof. Ver Bunt, Batavia, Java, who gave me this photograph.

if not unknown. That of course suggests that gangosa may be a manifestation of syphilis or perhaps of some separate infectious condition. Some writers have expressed the belief that the process originates in the mucous membrane, such as that of the soft palate, and that it extends from there outward (Stitt, 1929).

Schöbl (1928) stated that in some of his monkeys inoculated with the virus of yaws he produced lesions of the nasal region closely resembling gangosa as seen in man. His explanation of the pathogenesis of gangosa is that in an infected animal an ulcer develops on the skin of or inside the nose, that the animal becomes allergic as a result of the infection and that finally the ulcer produces an intense

destruction of tissue, even including bone, extending from the skin to the mucous lining of the nasopharynx. Schöbl expressed the belief that in some animals immunity develops, as will be shown later in this paper, and in such cases superinfection would fail.

Histologic Aspects of the Late Ulcers of Yaws and of Gangosa.—Histologic study of the late lesions has received less attention than that of the papillomas of the secondary stage. Hallenberger and Strong and Shattuck (1930) each considered it at some length. What is found is practically the picture seen in any granulating ulcer, which may be more or less modified by the amount of secondary infection: necrosis and ulceration, infiltration of the underlying tissue with lymphocytes, plasma cells, leukocytes, fibroblasts and sometimes giant cells and new growth of capillaries. There may be a perivascular infiltration of "small cells." Spirochetes are said to have been demonstrated in several cases of gangosa by Baermann and others. Hallenberger stated that the histologic picture of the ulcers of late yaws is very much like that of comparable lesions in syphilis; the classic alteration of blood vessels in syphilis is the most important criterion for the differential diagnosis of its late lesions from those of frambesia. In a histologic study of 50 cases, he made a diagnosis of frambesia in 49 and of syphilis in only 1. But in old syphilitic conditions the characteristic periarteritis and endarteritis cannot always be demonstrated, as I have often seen myself. Also in simple chronic granulating ulcers considerable change in the vessels may occur. It appears, then, that in a series of ulcers due to yaws there would probably be less change in the blood vessels than in a similar series in cases of syphilis but that the diagnosis in a single case would be very uncertain.

Goundou.—Goundou, or gundu, is the name given to a hyperostosis of the bones on the sides of the nose, sometimes likened to horns. Apparently it is seen most often in Negroes. Many observers have regarded it as a late manifestation of yaws, but others have not. Hallenberger stated that it is a peculiar thickening of the nasal process of the superior maxillary bone due to periostitis ossificans. He regarded yaws as its cause. In 1930 Strong and Shattuck published a report in which they discussed goundou and gave a review of the literature.

Juxta-Articular Nodules.—Juxta-articular nodules owe their name to Jeanselme. They have been fully described by Strong and Shattuck (1930), who gave a complete bibliography on the subject. In the following account I have attempted to condense the facts, chiefly those given by Strong and Shattuck.

Juxta-articular nodules are firm subcutaneous nodular masses, usually situated near joints of the extremities. They may attain the size of an egg. Essentially they consist of layers of connective tissue

enclosing a central necrotic mass. The central part contains leukocytes and many large mononuclear foamlike phagocytic cells. In the connective tissue layers there may be some periarteritis and endarteritis. In the cases studied by Gutierrez (1925) the nodes consisted of cellular connective tissue. Most observers have not seen organisms in the nodes. Strong and Shattuck did not observe any organisms, though all kinds of technical methods were employed. A few observers claim to have demonstrated spirochetes (cited by Baermann). These nodules have been attributed to a fungus of the Nocardia group, to syphilis and to yaws. The filarial worm Onchocerca produces very similar tumors (Strong and Shattuck). Evidently, there are various causes for the production of nodes of this sort. Many observers have found them to be frequent in localities where yaws is common and have regarded them as a late manifestation of yaws.

Aneurysm.—Many, if not most, writers on yaws have not mentioned aneurysm of the aorta. When it has been mentioned, the number of cases reported has usually been so small as to be without significance (Harley, Wilson and Mathis, Wilson, Hunt and Johnson, Macfie). However, Lambert stated that aneurysm and aortic disease are often seen in Fijians, among whom yaws is almost universal, while syphilis is almost unknown. The force of Lambert's statement seemed to me to be greatly lessened when he said that syphilis is frequent in East Indians and other Asiatics who have come to the same islands. A discussion of conditions in Fiji with regard to the occurrence of yaws and syphilis is found in connection with the papers of Manson-Bahr, Stannus and Powell.

The most extensive work on aneurysm and disease of the aorta in possible cases of yaws was that of Choisser in his report on 700 autopsies made in Haiti, which I shall summarize briefly: Most characteristic of yaws, Choisser stated, are patches of fatty degeneration of the aorta, beginning in the intima about 5 mm. above the valves, and in linear scars, and sometimes extending so as to involve the entire aorta in extensive atheroma. The valves of the heart are not often involved. He noted 8 cases of aneurysm of the aorta, 1 case of gumma of the brain and 1 of cerebral hemorrhage. Opalescent patches in the pericardium and endocardium, a flabby myocardium and small scars in the liver were noted. Choisser also stated that spontaneous cerebral hemorrhage (4 cases) is not infrequent in young adults with clinical histories and symptoms of yaws, but he did not describe the symptoms.

In estimating the significance of Choisser's studies, one should inquire whether or not he could possibly have been certain that he was dealing with yaws. He said that his patients had "a negative history of syphilitic infection and no evidence of scars on the genitalia." Referring to the changes of the aorta he said that "the only other clue to the infection is the scar of the mother yaw." Concerning some of his

patients with aneurysms he said that they gave histories of yaws in childhood or years previously. The evidence consisted, therefore, of statements found in the clinical histories, in the absence of genital scars and in the presence of scars attributed to a previous attack of yaws. If any of the subjects showed the characteristic papillomas of yaws while under observation, Choisser did not mention it. His autopsies were made at the Haitian General Hospital, Port au Prince, which is a seaport where syphilis is conceded to prevail. The evidence that the aneurysms and other lesions described by Choisser were due to yaws does not seem to me to be convincing (see the article by Koltes and Albrecht on the prevalence of syphilis in Haiti).

Weller has recently studied the aorta in 169 cases at the Haitian General Hospital which Chambers selected from what seemed to be probable cases of "treponematosis." One hundred and eleven specimens (66.8 per cent) showed histologic lesions similar to those of syphilis. Ninety-six of these were stained for spirochetes, and positive results were obtained in 28 cases.

The significance of these results depends entirely on the reliability of the clinical histories and on the importance of old scars of the genitalia in the diagnosis of syphilis and of old scars on the surface of the body in general in the diagnosis of yaws.

In a small number of these cases (11) there was a genital scar with a history of syphilis but not of yaws. In another small group (14) there were scars due to yaws with a history of yaws but not of syphilis, and no genital scars were noted. Nine of the syphilitic patients and 11 of those with yaws showed the microscopic changes in the aorta that are considered to be characteristic of syphilis. The unusual frequency of aortic aneurysm was noted. Weller did not consider that his study offered proof of either the unity or the duality of yaws and syphilis. An account of this work will appear in the *Transactions of the Association of American Physicians* for 1935. Dr. Weller has kindly allowed me to read an abstract of the paper and to publish this note in advance.

Other Conditions.—Tabes dorsalis and dementia paralytica are not mentioned in many reports on yaws; in many other cases the rarity of these diseases in regions where yaws is prevalent is noted. As far as I can learn, nowhere but in Fiji has yaws been assigned as a frequent cause of these conditions (Lambert). The remarks on conditions in Fiji made in connection with aneurysm of the aorta apply also in this paragraph. However, these forms of neurosyphilis are said by some to be decidedly rarer in colored races than in white races. The possibility that the frequent malaria of the tropics exercises a restraining influence on their development and the possibility that neurosyphilis may be due to a strain of spirochete with special affinities for the nervous

system suggest fields for study of uncommon interest, but not included within the scope of this paper. Diseases of the eye and alopecia are not usually mentioned as being frequent in cases of yaws.

INOCULATION

Human Beings.—Infection of human beings with yaws has been done with success by numerous experimenters by inoculation with material derived from patients with yaws. The results are cited by Ashburn and Craig and by many other writers.

Monkeys.—In monkeys inoculated with material from papules of yaws of human beings which contained the spirochetes, local lesions usually developed that were somewhat like those seen in human subjects and that also contained spirochetes. Inoculations were made subcutaneously or by applying serum to an abrasion. Secondary lesions seemed to occur rarely (see Ashburn and Craig, who also cited the previous work of Castellani and of Neisser and his colleagues), but Baermann saw secondary lesions repeatedly. The monkeys used were animals of the genuses Semnopithecus, Macacus and Cynomolgus and a few Gibbons and orang-utans. The incubation period varied from about fourteen days to more than ninety days. The spirochetes might be present in the spleen and lymphatic glands (Castellani) and in the bone marrow (Neisser and others). Numerous other investigators have made successful inoculations in monkeys (Nichols, White and Tyzzer, Schamberg and Klauder, Schöbl and his colleagues, Hoffmann). The reports of autopsies as recorded for infected monkeys have not included mention of lesions of the internal viscera (Ashburn and Craig, Schöbl). In the course of a large number of inoculations of monkeys (Cynomolgus) in Manila, Schöbl (1928) rarely saw spontaneous metastatic lesions other than those occurring through the local lymphatic vessels. However, he was able to produce distant metastases by superinfection. The metastatic lesions that he produced were not as numerous or as extensive as those that are often seen in human beings. In general Schöbl found these monkeys more resistant to yaws than man, and the lesions healed more promptly. Spirochetes were detected in the regional lymphatic glands only in cases of active yaws and not always in them. He saw no evidence that a latent infection existed in the lymph glands, but the spirochetes survived dormant in the skin. He stated that several types of lesions seen in man were reproduced in his monkeys, as has been mentioned with regard to hyperkeratosis and gangosa.

Rabbits.—Rabbits were used successfully for inoculation with the virus of yaws first by Nichols and subsequently by Reasoner, Brown and Pearce, Jahnel and Lange and Matsumoto and his colleagues. Numerous experiments were reported recently by Turner, Chambers

and Chesney, who gave references to the work done previously. They obtained successful inoculations with material from 8 different patients with undoubted clinical yaws in Haiti. At the same time rabbits were successfully inoculated with material from a Haitian Negro with a typical hunterian penile chancre; this and six other strains of syphilis from sources in the United States and Europe were used for comparison with those obtained from the rabbits infected with yaws. It was found, as others had previously claimed, that yaws was more difficult to propagate than syphilis. In rabbits the average incubation period was longer in yaws (thirty-eight and six-tenth days). As Brown and Pearce had already noted, and as was corroborated by most though not all observers, the inoculated testicle showed scattered miliary granules in its body, in the tunic or the epididymis; the miliary lesions consisted of large and small lymphocytes and many eosinophils. Spirochetes were demonstrated in the active lesions, which lasted several weeks and slowly retrogressed. The character of the results remained the same with the different strains and with the lapse of considerable time, indicating that there was no modification of the virus by repeated passage through rabbits (in one strain through fifteen generations of rabbits). The strain of syphilis recovered in Haiti gave results in the testicles of rabbits like those seen with other strains of syphilis, with great enlargement and induration, and the number of positive results from inoculation was much larger than with yaws. A considerable portion of the rabbits inoculated with yaws gave negative or slight reactions. Occasionally a rabbit gave a reaction as severe as that seen in the rabbits inoculated with syphilitic material. In rabbits intracutaneous inoculation with the virus of yaws produced erythema, desquamation or enlargement of the papillae, owing to collections of lymphocytes, not like the button-like lesion produced in syphilis of the rabbit's skin. Inoculations in the testis produced metastasis to the uninoculated testis less often than was the case with syphilis. None of 87 animals inoculated with the virus of yaws and carefully observed showed lesions indicating generalization of the infection in the bones, periosteum, skin and eyes; whereas lesions of that type were seen in rabbits inoculated with the Haitian strain of spirochetes of syphilis. Hashiguchi, however, according to Matsumoto observed lesions of the skin, bone and eyes in a fair proportion of rabbits inoculated with the virus of yaws.

Manteufel and his colleagues stated that in the beginning the strain of organisms of yaws with which they worked produced changes in the testicles of rabbits that were notably milder than those produced by inoculation with the organisms of syphilis. But gradually their strain of organisms of yaws came to produce results like those seen in rabbits with syphilis (large masses in the testicle; deep, hard chancres)

except that the rabbits with yaws after healing of the manifest lesions only exceptionally showed inoculable virus in the glands, while it was almost always shown by rabbits with syphilis.

Using a strain of organisms of yaws obtained in Sumatra, Hoffmann produced in rabbits a granular periorchitis like that described by Brown and Pearce and nodules containing numerous spirochetes. He observed unilateral nodular infiltrations consisting of lymphocytes and plasma cells involving the adventitia and media and even the intima of the small veins; he considered that this condition differed from the phlebitis of syphilis.

Some Japanese investigators have stated that yaws can be transmitted to guinea-pigs by inoculation, the prepuce being the most favorable location. It is said that the local lesion is different from that produced by inoculations with the virus of syphilis (Tani and Ogiuti) and also that mice and rats may be inoculated with the spirochetes of yaws, and that the organisms may be demonstrated in some of the viscera for a long time thereafter (Misaizu).

IMMUNITY TO YAWS

Rat has said that second attacks of yaws occur but are rare. He also stated that in places where yaws is endemic "it generally attacks children, and experience shows that the disease runs a milder course than in the later years of life. So convinced of this are parents in certain parts of Africa that every facility is given to contract the disease in infancy, and even inoculation is resorted to in order to ensure this." Sellards said that "at Yamasá in the Dominican Republic the parents make a practice of freely exposing children to the disease because they feel that the sequellae, especially clavos, are less likely to be severe when the disease develops during infancy." Mattlet observed that near Lake Tanganika in Africa mothers inoculate infants with material from persons with pian to ward off tertiary complications; in infants the secondary eruption is excessively florid. According to Stitt (1928), inoculation to procure immunity is practiced by natives of Guinea, and Manson-Bahr said that this has long been done in Fiji. In Java I met physicians who informed me that the natives believe that an attack of yaws confers immunity and other physicians who had not heard of any such belief. Among those who have had large experience with yaws the belief seemed fairly general that immunity is developed. Hermans cited numerous examples of this belief.

There are also reports of cases in which reinfection or superinfection has occurred, though it happens rarely (Baermann).

Sellards, Lacy and Schöbl showed that volunteers could be infected with yaws. From four to six weeks later and while secondary lesions were present, they were again inoculated, and granulomas resulted.

Sellards and Goodpasture (1923) and Lacy and Sellards (1926) observed that in subjects who had had yaws some months or years previously (some of them having had treatment) reinoculation sometimes gave positive results, more often abortive lesions or no lesions at all. These experiments indicated that the development of immunity requires a long time. Baermann cited experiments by Castellani, Neisser and others that seemed to show that monkeys that are successfully inoculated acquire immunity against yaws; he also considered and discussed the possibility that an apparent immunity may be due to latent infection.

Continuing the studies for which their inoculation of monkeys with the virus of yaws laid the foundation, Schöbl and his colleagues performed an enormous amount of experimental work on immunity against yaws and syphilis, using several hundred monkeys. Their work had the merit of having been done in the tropics as well as having been conducted on an animal as nearly related to man as possible. The results were published in various numbers of the *Philippine Journal of Science* from 1928 to 1931. They were summarized in the paper of Schöbl and Hasselmann.

Schöbl stated that in monkeys inoculated with the organisms of yaws a positive (Wassermann, Kahn) reaction of the blood serum might develop (Garcia). A strongly positive reaction developed when the local lesion was marked and after repeated outbreaks in the animal; when there were slight local lesions or late lesions, the reaction was likely to be weak. The serum reaction was manifested in an early positive phase after the first inoculation, then a negative phase and then a second positive phase, whether more lesions appeared or not.

A condition resembling immunity might ensue, as was indicated when a fresh inoculation with infectious material was followed by a negative result. Immunity in inoculated monkeys usually appeared about six or seven months after the original inoculation. (The slow development of immunity may explain the conflicting results of other observers.) Schöbl observed that the condition of resistance to superinfection was effective in proportion to the intensity of the early lesions in yaws and the number of invading organisms. He expressed the belief that his results were in harmony with the principles established by Brown and Pearce for experimental syphilis, which he stated as follows: "The number of the invading treponemas during the early stage stands in direct proportion to the degree of immunity that subsequently develops. It stands in inverse proportion to the time necessary for the development of immunity." The immunity endured for a long time, probably throughout the life of the monkey; it might persist after the serum reactions became negative. Schöbl prepared a vaccine consisting of killed parasites from experimental lesions of yaws

in monkeys. Injections of that vaccine produced in monkeys positive reactions of the serum the strength of which was in proportion to the number of organisms introduced. Schöbl and his colleagues stated further that monkeys given injections of the vaccine were made immune so that they resisted inoculations with the living organisms of yaws.

CROSS-IMMUNITY BETWEEN YAWS AND SYPHILIS

Various observers from widely separated points have expressed the opinion, based on clinical studies, that infection with one of these diseases confers a certain amount of immunity against the other (Wilson and Mathis in Haiti, Manson-Bahr and Lambert in Fiji, Parham in Samoa and Connolly in East Africa); the more common opinion is that an attack of yaws sometimes gives immunity against syphilis. However, the evidence is somewhat conflicting (Mattlet, van den Branden and Dubois, Powell). MacCallum related a curious incident: "St. Johnstone examined carefully a labor battalion of Fijiians which was sent to France during the war. They all had yaws but no syphilis. On their return there were many cases of gonorrhea, but none of syphilis." Some critics have regarded the reports from these islands as unconvincing and have questioned that the native population is as nearly free from syphilis as is alleged. It is known that the East Indians and Chinese in Fiji have syphilis (Powell, Stannus). Strong and Shattuck, and Baermann have given good summaries of what was known of the immunologic relations of yaws and syphilis up to 1930. In the present review I shall refer only to part of the work published. Several observers have reported the occurrence of one of these diseases in persons who had already had the other; for instance, Goodman saw yaws in a child who also had hereditary syphilis. Castellani, and Neisser and his colleagues found that monkeys that had been infected with yaws were refractory to yaws but susceptible to syphilis. Levaditi and Nattan-Larrier were successful in infecting monkeys with yaws but were unable to transmit yaws to monkeys which had previously been infected with syphilis. Nichols inoculated a small series of rabbits with yaws, and part of them were treated. After intervals of from ninety days to more than a year they were inoculated with an active strain of syphilis. More than half of the animals proved refractory to the second inoculation. About 25 persons with dementia paralytica were inoculated by Jahnel and Lange (1928) with a virus of yaws from infected rabbits, using strains from America and from Sumatra. The results were negative in all but 1 case (Sumatra strain), in which an abortive lesion resulted. Jahnel and Lange have given a good summary of the characters of yaws and its immunology as reported up to 1928. They discussed the properties of different strains of the virus

of yaws and the time factor in the production of immunity. They suggested that yaws and syphilis express the extremes of a group of closely related viruses in which endemic syphilis, which is usually of extragenital origin, may be an intermediate process.

Manteufel considered some of these experiments and others and reviewed statements to the effect that a strain of syphilis has been said to protect animals from inoculation only with the same strain (Kolle and Schlossberger); that strains of organisms of yaws and of syphilis that did not have comparable degrees of virulence have been used in cross-immunity experiments and also that strains of the virus of yaws seem to acquire greater pathogenicity with repeated passages (see the discussion under inoculation of rabbits). Manteufel then expressed the opinion that experiments in cross-immunity do not give convincing evidence for or against the nonidentity of yaws and syphilis.

Schöbl expressed the belief that fundamental differences exist between yaws and syphilis and that the two diseases may coexist in one animal. Nevertheless he noted a certain amount of both serologic and immunologic reciprocity between them, and he agreed that biologically the organisms belong to the same group. He and his colleagues experimented with monkeys, testing them in various ways with the Nichols strain of syphilis obtained from infected rabbits. This strain inoculated into the skin of the eyebrow or scrotum of the monkey gave a slight local reaction, soon healing, while the regional lymphatic glands continued to harbor viable organisms (tested by inoculation of rabbits in the testis). It is impossible to give here more than an indication of the kind of experiments made; for details the original articles must be consulted (Schöbl, Schöbl and Hasselmann). Schöbl stated that monkeys that had been rendered immune against yaws by inoculation with living organisms of yaws "or by the injection of the lifeless vaccine [referred to previously] proved refractory to inoculation with syphilis a year later, and some gave earlier, slight or no local reaction and showed in the lymphatic glands no viable organisms, provided that the immunity from yaws infection had been given sufficient time to fully develop." From other experiments carried out on similar lines it was concluded that monkeys that were first inoculated with syphilitic material became resistant to subsequent inoculation with the spirochetes of yaws. In these tests the time factor and the amount and kind of material injected were of fundamental importance. Schöbl concluded that a reciprocal immunity existed that was a group immunity against yaws and syphilis and that a homologous immunity also existed that developed earlier than the heterologous group immunity. One strain of yaws that was employed continuously for six years and repeatedly passed through monkeys kept its characters unaltered.

Schöbl also noted that the strain of syphilis (Nichols) continued to produce a local sclerosis in monkeys as long as it was used.

Dr. Schöbl has kindly examined and corrected the foregoing account of the work of himself and his colleagues. Obviously his statements regarding his later experiments suggest possibilities of immense importance. It is to be hoped that these experiments will be repeated and amplified, strains of yaws and syphilis from new sources being employed.

Certain Japanese investigators reported that they failed to find evidence of cross-immunity between yaws and syphilis. Matsumoto and his colleagues stated that rabbits might be superinfected with yaws within seventy-six days of the first inoculation, while superinfection usually failed eight months after the first infection. But in animals infected with yaws that received thorough treatment with arsphenamine, reinoculation gave positive results twenty months after infection. They observed that syphilitic rabbits were usually susceptible to inoculation with yaws. Rabbits that had been cured of syphilis with arsphenamine were usually susceptible to yaws. Six of 10 rabbits that were not susceptible to superinfection with syphilis (even with a heterologous strain) were still susceptible to inoculation with the organisms of yaws. Kato infected rabbits with yaws; they were then superinfected three times and were found to be immune against yaws. Thirty-one days after the third superinfection, spirochetes of syphilis, in part highly diluted, were introduced into the back. The inoculations were said to have given uniformly positive results, with more or less prolongation of incubation. Rabbits were infected with yaws and after from one hundred and two to three hundred and eight-nine days were cured with arsphenamine. Twenty days later these rabbits were inoculated intravenousiy with an emulsion of syphilitic virus, and later all of them presented generalized lesions due to syphilis. More recently Misaizu, using rats and mice, first infected the animals with the spirochetes of yaws, then treated them with arsphenamine and later reinfected them with the spirochetes of yaws. He observed no evidence that specific immunity was produced by the first inoculation. Such experiments as were performed to test the development of cross-immunity between yaws and syphilis gave negative results.

SUMMARY AND DISCUSSION

A few years ago I began examining the evidence bearing on the relations of yaws and syphilis and had the advantage of being without any preconceived opinion. It soon became clear that some acquaintance with the appearance of yaws was necessary, and I visited the tropical islands of Haiti and Java and the Philippines (Manila). I saw a

moderate number of patients with yaws (from 300 to 400), mostly on a single occasion only. Practically every type of lesion that I have seen described was observed, but there were only a small number of instances of obvious bone disease. I was deeply impressed with the fact that yaws is only one of many problems confronting physicians in the tropics, along with dysentery, beriberi, tuberculosis, smallpox, leprosy and sometimes bubonic plague and with malaria and worms always to the front.

Acute yaws is comparatively easy to manage by treatment, though what the final results of the treatment will be cannot yet be determined. The natives, having observed the results of treatment, appear at the clinics voluntarily in large numbers and bring their children. Patients with acute yaws seem not to come to autopsy. Autopsies in the tropics can be made with modern technical methods only at hospitals in large cities, where it is difficult to exclude the possibility that syphilis may be present.

Beginning with Rat's monograph and even in earlier treatises, yaws and syphilis have been compared many times, the points of resemblance or difference often being arranged in parallel columns. Most of these points have been mentioned in the preceding paragraphs. Because of a lack of large experience with yaws and with dermatologic diseases in general, I have probably made some mistakes. In this following summary, I shall confine myself chiefly to a discussion of the pathologic anatomy and the histologic picture.

The primary lesions of yaws and of syphilis differ decidedly in their histologic features, according to the small amount of information available. Final conclusions cannot be made until more material is at hand.

The secondary lesions of acute florid yaws differ decidedly in their gross appearance from most secondary eruptions of syphilis, though syphilis rarely causes lesions like those of yaws, and yaws is said sometimes to cause eruptions like those of syphilis. Histologically, typical lesions of yaws are characterized by the presence of spirochetes, chiefly among the epithelial cells, by marked proliferation of the epithelium downward, by the large number of leukocytes that penetrate the epidermis and by the slight amount of involvement of blood vessels. Thus, the papules of yaws differ from most syphilitic lesions, but occasionally condyloma and some of the cutaneous lesions of syphilis may give fairly similar pictures.

Late ulcers of yaws and those of syphilis are so much alike that a diagnosis between them is frequently impossible. It has sometimes seemed to me that in certain tropical regions similar conditions were likely to be called syphilis in the city and yaws in the country. Such information as is available indicates that the differences in the histologic

picture are not marked enough to be decisive in many if not most cases. However, further study must be made before a definite conclusion can be reached.

As to involvement of bone, it seems to me that it must be admitted that roentgenograms show that the bones are often affected in yaws and that the pictures are often like those seen in cases of syphilis. As far as I can learn there has been little histologic study in these cases.

The evidence that has been presented to show that aneurysms of the aorta are caused by yaws appears to me to be unconvincing. It is probable that the internal viscera in general are not involved in yaws, but the autopsy evidence is insufficient.

Both clinical and experimental work indicate that an attack of yaws confers considerable immunity against a second infection.

Also, clinical observations and laboratory experiments suggest that a certain amount of cross-immunity between yaws and syphilis may be produced, but the statements are somewhat conflicting. Possibly some of the discrepancies seen in experiments on animals may be due to the use of infectious agents having different degrees of virulence or to the fact that the immunity tests were made later in some experiments than in others. More work is urgently needed, preferably on monkeys, in my opinion, and in a tropical climate.

Opinions on the relationship of yaws to syphilis differ widely. Yaws has been called syphilis of the tropics and stone-age syphilis; syphilis and yaws have been called brother and sister as well as twins. Castellani regarded them as wholly distinct infections, like tuberculosis and leprosy. Butler expressed the belief that yaws is syphilis. An ingenious theory was suggested recently in a monograph by Essed: Syphilis was an old disease in Europe; yaws was imported into Europe from America by the sailors accompanying Columbus; it apparently has disappeared from Europe and has reappeared from time to time under various names; some endemic syphilis is really yaws.

More than forty years ago Hutchinson remarked that physicians practicing in the tropics almost always consider yaws and syphilis to be different diseases. I have discussed the matter with nearly fifty physicians in the islands, previously named, and my recollection is that almost without exception they recognized differences between yaws and syphilis; only a small number were noncommittal.

Apparently no one has recorded having actually witnessed the transformation of yaws to syphilis or of syphilis to yaws in man. Convincing evidence could hardly be secured except under the conditions of a laboratory experiment. Endemic syphilis, as observed by von Düring Pasha in Asia Minor, in an unusually degraded population resembles yaws in some particulars, but resemblance does not constitute identity. There is abundant evidence to show that Negroes in the

tropics may have syphilis of the ordinary form (van den Branden and Dubois), except that tabes and dementia paralytica are usually said to be rare. Probably all will agree that the spirochetes of yaws and syphilis originally had the same spirochete for an ancestor. The evidence that is available gives me the impression that the spirochete of either yaws or syphilis has undergone a functional but not a morphologic mutation in some human host, giving rise to the other infection, and that the resemblances between the two infections indicate that the new infection has evolved from the older one in comparatively recent times.

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Notes and News

University News, Promotions, Resignations, Appointments, Deaths, etc.—William H. Park, director of the bureau of laboratories of the health department of New York City since the establishment of the bureau in 1894, has been awarded the Roosevelt Medal for 1935 for "distinguished service in the administration of public office."

In Georgetown University, G. J. Brilmyer has been appointed professor, and I. A. Simpson and H. V. Connerty assistant professors, of pathology and parasitology.

The Trudeau Medal of the National Tuberculosis Association has been awarded to L. U. Gardner in recognition of his work on tuberculosis, particularly the relation between tuberculosis and silicosis.

Esmond R. Long, director of the laboratory of the Henry Phipps Institute of the University of Pennsylvania, has been made director of the institute. Charles J. Hatfield, formerly director, will be associate director and chairman of the board of directors. Henry R. M. Landis will have charge of the clinical and sociologic departments.

Marion Dorset, biochemist in the United States Department of Agriculture, well known for his work on serum against hog cholera and author of many contributions of value to the livestock, meat and dairy industries and to public health, has died at the age of 63.

An oil portrait of Milton C. Winternitz, who has retired from the deanship of the medical school of Yale University after fifteen years' service, has been presented to the school by the student body.

Oswald T. Avery, of the hospital of the Rockefeller Institute for Medical Research, has received the honorary degree of LL.D. from McGill University.

Morris Rakieten has been appointed assistant professor of bacteriology in Long Island College of Medicine, Brooklyn.

Harry Goldblatt has been promoted to professor of experimental pathology in Western Reserve University, Cleveland.

Gustav Ruediger, formerly professor of pathology in the University of North Dakota, director of the Hygienic Institute at LaSalle, Ill., and director of the hygienic laboratory of the University of Nevada, has died in Pasadena, Calif., of tuberculosis at the age of 59.

Sanford V. Larkey, librarian and assistant professor of medical history and bibliography in the medical school of the University of California, has been appointed librarian of the Welch Medical Library of Johns Hopkins University, succeeding the late Fielding H. Garrison.

Herbert S. Gasser, professor of physiology in Cornell University Medical College, has been appointed director of the Rockefeller Institute for Medical Research to succeed Simon Flexner, who will retire.

Frederick F. Russell has resigned as director of the International Health Division of the Rockefeller Foundation and will be succeeded by Wilbur A. Sawyer, associate director. Dr. Russell will be lecturer on preventive medicine and hygiene at the Harvard University Medical School.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

PAROSMIA IN TUMOROUS INVOLVEMENT OF THE OLFACTORY BULBS AND NERVES. H. A. PASKIND, Arch. Neurol. & Psychiat. **33**:835, 1935.

A woman aged 45, three years after an operation for carcinoma of the breast, complained of headache, dizziness and reeling gait with a tendency to fall to the left. In addition, she continuously smelled an unpleasant odor for two weeks and had left homonymous hemianopia for three days. A carcinoma of the left cerebellar lobe was diagnosed and removed. Necropsy revealed carcinomatous masses throughout the central nervous system and viscera and, in addition, a carcinomatous nodule in each olfactory bulb. It also invaded the olfactory nerves, some of which were swollen or degenerated. Paskind emphasizes the extreme rarity of continuous parosmia caused by a tumor of the olfactory tract. He cites only three other instances, in which the disturbances of the sense of smell were due respectively to carcinoma, meningioma and glioma involving the olfactory tractor bulb.

GEORGE B. HASSIN.

THE METABOLISM OF ISOLATED SURVIVING TISSUES FROM ANIMALS RENDERED HYPERTHYROID WITH THYROXINE. D. MCEACHERN, Bull. Johns Hopkins Hosp. **56**:145, 1935.

Representative tissues isolated from hyperthyroid animals continue to show increased consumption of oxygen. The increase in tissue respiration is only roughly proportional to the increase in total consumption of oxygen by the intact hyperthyroid animal. The increase of tissue respiration is not so great as would be expected from the increase of metabolism in the intact animal. The increase in the respiration of hyperthyroid tissue is not carried on by any new or abnormal respiratory mechanism in the cell. An increase of tissue glycolysis is not the fundamental cause of the increased consumption of oxygen. Cyanide, fluoride and mono-iodo-acetic acid reduce the respiration of hyperthyroid tissues but do not affect the fundamental mechanism which makes an increased supply of oxygen necessary to the organism. Iodine, when added directly to the tissue, has no specific effect on the increased respiration due to hyperthyroidism. Hepatic and renal tissues from hyperthyroid animals have no lessened capacity to oxidize various substrates (lactate, pyruvate, succinate). Hyperthyroid muscle has a greater capacity to oxidize these substrates than has normal muscle.

FROM THE AUTHOR'S CONCLUSIONS.

THE TESTIS HORMONE. C. R. MOORE, J. A. M. A. **104**:1405, 1935.

The principal sources of testicular hormone at present are the testicles of large mammals and human urine. The hormone is obtained from the lipoid fraction and has been sufficiently purified to yield crystals of high potency. It appears chemically to be a ketone-alcohol; the only known method of detecting its presence is by the reaction produced in suitable animals. It is secreted continuously (or periodically) in different animals, and the secretion is largely under the control of the pituitary gland. It is uncertain whether more than one hormone is selected by the testis. Its clinical use is questionable; its primary function is the control of the accessory reproductive organs; it is not a testicular stimulant.

FROM THE AUTHOR'S SUMMARY.

ACUTE EXPERIMENTAL STOMATITIS IN DOGS WITH LEUCOPENIA. D. K. MILLER and C. P. RHOADS, J. Exper. Med. **61**:173, 1935.

An ulcerative stomatitis associated with leukopenia and granulopenia can be induced in dogs by means of a diet causing black tongue. The decrease in the number of circulating leukocytes is due to a suppression of the maturation of the erythropoietic elements of the bone marrow. The changes as a whole have a resemblance to those occurring in human beings with acute agranulocytosis.

FROM THE AUTHORS' SUMMARY.

Pathologic Anatomy

REACTION OF PULMONARY TISSUE TO LIPIODOL. R. D. WRIGHT, Am. J. Path. **11**:497, 1935.

The reaction to iodized poppy-seed oil 40 per cent retained for long periods in the bronchi is the development of lipophages from the supporting connective tissues. No epithelial reaction occurs.

FROM THE AUTHOR'S SUMMARY.

INFARCTION OF THE LIVER. I. J. PASS, Am. J. Path. **11**:503, 1935.

A review of the literature on infarction of the liver with a report of two additional cases is given.

FROM THE AUTHOR'S SUMMARY.

BASOPHILIC DEGENERATION OF THE HEART MUSCLE. M. E. HAUMEDER, Am. J. Path. **11**:535, 1935.

A peculiar lesion of the heart muscle is described under the term "basophilic degeneration." The most frequent sites of the lesion were the septum, the left ventricle and a combination of the septum and the left ventricle. Staining reactions showed that the areas contained mucin as well as a component related to glycogen. Hematoxylin and eosin was the most valuable stain because it clearly differentiated the areas of basophilic degeneration.

FROM THE AUTHOR'S SUMMARY.

HEART BLOCK DUE TO CALCAREOUS LESIONS OF THE BUNDLES OF HIS. W. M. YATER and V. H. CORNELL, Ann. Int. Med. **8**:777, 1935.

Of the forty-seven cases of complete heart block authentically reported in the literature nine were due to fibrocalcareous or calcareous lesions of the bundles of His. Such calcium depositions were commonly seen at the base of the aortic (anterior) leaflet of the mitral valve, extending out into the membranous portion of the interventricular septum. They occurred late in life—no cases in persons below the age of 50; five instances in those in the eighth decade of life. All the patients had Adams-Stokes attacks. Sclerosis of the coronary arteries did not parallel the local lesion nor was there evidence of fibrosis of the myocardium except in two instances. By serial sections the authors demonstrated that a bar of calcium deposit in the usual location in the heart of an army officer who also had a syphilitic aneurysm of the aorta actually replaced or invaded all of the bundle of His. It was concluded that such deposition of calcium is due to stress and strain, since the main mass of the heart hangs from the area of the membranous septum. The bundle of His above and below the point of injury was found to be normal, demonstrating the non-nervous structure of this system.

FRANK R. MENNE.

THE CELLULAR REACTIONS TO ACETONE-SOLUBLE FAT FROM MYCOBACTERIA AND STREPTOCOCCI. K. C. SMITHBURN and F. R. SABIN, J. Exper. Med. **61**:771, 1935.

The acetone-soluble fat of tubercle bacilli, when injected into normal animals, produces a profound cellular reaction. The reaction involves every type of connective tissue cell. Hemorrhage and formation of adhesions and of tuberculous tissue occur. The extent of the reaction is roughly proportional to the amount of material injected. The reaction induced by the lipoid is much less extensive and much simpler when the material is neutralized with alkali. Neutralization of the acetone-soluble fat, or of phthioic acid, does not diminish the tuberculogenic property. Acetone-soluble fat from streptococci is likewise extremely irritating but does not produce tuberculous tissue.

FROM THE AUTHORS' SUMMARY.

RUPTURE OF THE RENAL PELVIS. BENJAMIN S. ABESHOUSE, Surg., Gynec. & Obst. **60**:710, 1935.

From a review of 64 cases from the literature and three from his own records Abeshouse concludes that rupture of the renal pelvis proper, traumatic or spontaneous, is relatively rare. Traumatic rupture is usually linear and radial. The external trauma may vary from a crushing injury to an indirect blow. Spontaneous rupture nearly always occurs in a kidney already the seat of chronic pyelonephritis or in one the pelvis of which is dilated from obstruction lower down. Rupture is the result of sudden or gradual increase in the back pressure caused by obstruction. Perforation of the pelvis from necrosis due to an impacted calculus is also frequent. An already weakened pelvis may be ruptured by instruments or from increased pressure during employment of the syringe method of pyelography. Perforation has followed the injection of a strong alkali by mistake during pyelography or renal lavage.

WARREN C. HUNTER.

FIBRINOUS BALLS IN THE URINARY BLADDER. F. P. WEBER, J. Path. & Bact. **40**:351, 1935.

In a man with a malignant renal tumor the urinary bladder after death contained four fibrinous balls, the largest about the size of a hen's egg. Apparently the fibrin was deposited from the urine, perhaps around fragments from the tumor of the left kidney.

SIMPLE SUPERFICIAL ESOPHAGEAL CAST. T. C. PATTERSON, J. Path. & Bact. **40**:559, 1935.

Exfoliation of the epidermal lining of the gullet occurs during health, neither infection nor caustic action being causally related. There is usually a history of some earlier mild trauma such as the continued abuse of alcohol, especially strong spirits, the swallowing of hot drinks, the taking of acrid food or the bolting of large mouthfuls. Minor injuries due to foreign bodies are also recorded. Pre-existing cardiospasm and dilatation have sometimes been suspected, largely on the grounds of a history of dysphagia and some apparent obstruction to the passage of food, coupled with the fact that the esophagus had a greater than normal diameter. But this may easily have been the result of stretching of the flimsy tissue during slow spasmodic extrustion. Except in Memmi's case the histories contain little evidence of actual dilatation. In none of the cases is there any indication of syphilitic taint. The patients suffer only moderate and temporary discomfort and practically no shock. The extruded material consists only of the epidermal lining of the gullet, the separation occurring in the subepithelial zone, leaving the deeper parts everywhere intact. The cast is clean, uniformly grayish white, parchment-like and quite free from the foul, discolored, sloughy appearance and deep

penetration seen in corrosive poisoning and phlegmonous esophagitis. Complete and rapid recovery ensues. There is an entire absence of any tendency toward stenosis as a sequela. Very soon after the event the passage appears normal on direct esophagoscopy. New firm epithelium forms pari passu with the gradual separation of the cast. In Reichmann's case the forcible application of a metal sound to overcome the obstruction had no ill effect. Le Comte gave emetics with impunity. So slight is the upset that little treatment is necessary beyond judicious resting of the part and temporary restriction to bland fluid nourishment. As a counsel of perfection, rectal feeding has sometimes been carried out for a few days. A peculiar exfoliative tendency seems to be present in certain of the cases. In three cases casts were produced on more than one occasion; and in one of these there was a previous history of severe general eczema. The latter case is possibly analogous to that described by Sligh (1893-1894) in which a man of 36 gave a history of having been taken ill every year since infancy with shedding of the epidermis from the entire surface of the body including the finger-nails and toe-nails. In a few days the exposed new, soft, tender skin became sound and the man could resume work.

FROM THE AUTHOR'S CONCLUSIONS.

Microbiology and Parasitology

THE VIRUS OF INGUINAL LYMPHOGRANULOMA. J. T. TAMURA, J. Lab. & Clin. Med. **20**:393, 1935.

When pus from lymphogranuloma inguinale is planted in the medium devised by Maitland and his co-workers (*Brit. J. Exper. Path.* **13**:90, 1932) for the cultivation of vaccinia virus the medium becomes cloudy. The agent producing the cloudiness is transmissible in serial cultures, or serial cultures alternating with guinea-pig inoculations. This agent whether in the pus or in the cloudy supernatant culture fluid passes the Berkefeld N filter. The virus is stainable by Hosokawa's eosin-Giemsa method. The heated cultures have been used successfully in making diagnoses by the intradermal skin test and in inducing recoveries through subcutaneous inoculations. Also heated cultures have been used to produce antiserum. Although one can draw no definite conclusions from the few cases in which treatment with the antiserum has been studied the results justify further trial of serum therapy.

FROM THE AUTHOR'S SUMMARY.

A NEW VIRUS CAUSING LYMPHOCYTIC MENINGITIS. C. ARMSTRONG and J. G. WOOLEY, Pub. Health Rep. **50**:537, 1935.

The isolation of three similar strains of a newly described virus is reported. Spontaneous infection among stock monkeys has been demonstrated by the isolation of the virus from a noninoculated monkey and by the demonstration of specific antibodies in the serums of 5 of 44 such animals. The possibility that the virus may affect man is suggested since two of the recovered strains are possibly of human origin. The ready and even spontaneous infection of monkeys with the virus, together with the fact that human serums (3 from 166) possessing potent specific antibodies for the virus have been encountered, points in the same direction. As previously noted, the disease in monkeys resembles the human ailment designated as lymphocytic or aseptic meningitis, and serum collected from a person eleven months after a clinical attack of this disease gave strong protection against strains of the experimental virus. The finding of immunity in the serum of an exposed person giving no history suggesting this disease, however, indicates that immunity may develop in the absence of symptoms indicating involvement of the central nervous system.

FROM THE AUTHORS' SUMMARY.

SUBFREEZING TEMPERATURES IN PRESERVING MENINGOCOCCI. A. M. PABST, Pub. Health Rep. **50**:732, 1935.

Ten chosen strains of meningococci have been stored in neutral glycerin at —15 C. for two years with no apparent change in viability, morphology or serologic and biochemical characteristics. Two hundred and twenty-three strains have been stored at this temperature on dextrose agar slants both with and without glycerin, with no appreciable loss of viability in the eight months during which they have been under observation.

FROM THE AUTHOR'S SUMMARY.

THE GROWTH OF PSITTACOSIS VIRUS IN TISSUE CULTURES. J. O. W. BLAND and R. G. CANTI, J. Path. & Bact. **40**:231, 1935.

The virus of psittacosis was grown in cultures of embryonic chicken tissue. It infects both epithelial cells and fibroblasts. A description is given of the appearance of the intracellular colonies at various stages of their development: (*a*) in preparations stained by Giemsa's method, (*b*) in living cultures examined by dark-ground illumination and by transmitted light, and (*c*) in quick-motion cinematograph films. This study confirms the existence of a developmental cycle in the virus of psittacosis as previously described.

FROM THE AUTHORS' SUMMARY.

PSITTACOSIS IN THE DEVELOPING EGG. F. M. BURNET and P. M. ROUNTREE, J. Path. & Bact. **40**:471, 1935.

Psittacosis virus derived from Australian parrots is readily propagated in the developing egg. Large amounts of virus develop by infection of cells of the ectodermal epithelium, and a characteristic lesion develops. No infection of the embryo proper takes place, and the lesions of the egg membrane are as a rule rapidly resolved after the third or fourth day. The developmental changes in the appearance of the virus bodies described by Bedson and Bland can be well observed in impression preparations from infected egg membrane.

FROM THE AUTHORS' SUMMARY.

TUBERCULOUS MENINGITIS IN CHILDREN. J. W. S. BLACKLOCK and M. A. GRIFFIN, J. Path. & Bact. **40**:489, 1935.

Tuberculous meningitis is the most frequent form of meningitis in childhood and accounts for more deaths than all other forms of tuberculosis together. The primary site of infection in a series of 241 patients under 13 years was most frequently thoracic (73.9 per cent), then, in order, abdominal (22.8 per cent), cervical glandular (2.1 per cent) and unknown (1.2 per cent). There was little difference in the distribution according to sex, though meningitis following a primary thoracic lesion was slightly more frequent in girls, and that following primary abdominal tuberculosis was commoner in boys. Of the total number of patients 85.5 per cent were under 6 years of age. The incidence was highest in the late spring and early summer months. The frequent association of tuberculous meningitis and general miliary tuberculosis is discussed; either lesion alone is uncommon. The methods used for isolating and typing tubercle bacilli from the cerebrospinal fluid are described. Human strains were easier to isolate directly by culture than bovine. In one case of infection with a human strain the inoculated guinea-pig gave a negative result whereas the cultures were positive. From a clinical series of cases of cerebral tuberculosis 72 strains were isolated, of which 18.1 per cent were bovine, and from the primary lesions in an autopsy series 114 strains were obtained, of which 24.6 per cent were bovine. The highest percentage of bovine strains occurred in children in the third year of life in both series. The total percentage of bovine strains obtained for meningitis from both the aforenamed

series was 22.5 and for all forms of cerebral tuberculosis 22. This figure is compared with that found by other workers both in this country and abroad. A higher percentage of bovine infections was noted in country than in city children and a probable reason for this is given. Meningitis following primary thoracic lesions was nearly always due to the human type of bacillus, and that following primary abdominal lesions was usually due to the bovine type. From 3 cases of meningitis with the primary lesions verified at autopsy bovine strains were isolated. A case is described in which tubercle bacilli were isolated during life from the cerebrospinal fluid and in which tuberculomas were found post mortem but no meningitis. The bearing of this on the reported recoveries from tuberculous meningitis is discussed.

FROM THE AUTHORS' SUMMARY.

THE IMMATURE RABBIT AS AN EXPERIMENTAL URINARY AND FAECAL TYPHOID CARRIER: EFFECT OF HEXAMINE TREATMENT. M. COPLANS, J. Path. & Bact. **40**:521, 1935.

By the passage of a laboratory stock culture of Bacillus typhosus through a series of rabbits a strain of organisms was isolated which on intravenous injection proved pathogenic in immature rabbits, setting up fecal and urinary carrier conditions in a considerable proportion within the limits of the experiment (sixty-three days). All the twenty-seven controls proved to be infective on postmortem examination. An equal number of immature animals that were similarly inoculated were subsequently treated by oral administration of methenamine and the proportion of carriers, both urinary and fecal, was greatly reduced, no pathogenic organisms being isolated from those which survived the fifteenth to the sixty-third days. Another strain of the organism which after passage was eventually isolated from the feces of a rabbit was utilized for contaminating the green food of immature rabbits which were otherwise being normally fed. In two of ten animals so fed the organisms were excreted in the feces.

FROM THE AUTHOR'S SUMMARY.

THE SYPHILITIC VIRUS. W. NYKA, Ann. Inst. Pasteur **53**:243, 1934.

The agent of syphilis has two distinct morphologic aspects: the usual spirochete and a filamentous form, between which are a variety of other forms. The transmission of syphilis by the spirochetal form is transitory; the characteristic structural changes of the disease are due to the filamentous form. The spirochetal form is cytotropic and multiplies either in the cytoplasm or in the nucleus, in which the transition to the filamentous form occurs, although the transition occasionally occurs outside of the cell. Filaments multiply by transverse fission. The resulting fragments may develop as spirochetes. Multiplication within the cells destroys the latter. Hepatic cells and fibroblasts are only slightly susceptible, whereas lymphatic cells and nerve cells are quite susceptible. The filamentous form has heretofore been overlooked because of its weak staining properties.

FROM THE AUTHOR'S CONCLUSIONS.

MIXED STREPTOCOCCODIPHTHERITIC INFECTION. G. RAMON and M. DJOURICHITCH, Ann. Inst. Pasteur **53**:325, 1934.

By using guinea-pigs of standard weight and a virulent strain of the diphtheria bacillus mixed with streptococci or other organisms various data were secured. Certain hemolytic streptococci permitted death of animals with smaller amounts of emulsion of the diphtheria bacillus than killed control animals. Animals with anatoxin (toxoid) uniformly survived mixed injections. Animals given broth with diphtheria bacilli showed no effect, but streptococcus filtrates, as well as killed organisms, increased the mortality. The effect occurred only when mixtures were inoculated at the same site. Serial transfers in animals resulted neither in enhanced

virulence of the mixture nor in virulence or toxigenicity of the diphtheria bacillus used. The authors believe that the action is nonspecific, and that a similar stimulation accounts for the gravity of such mixed infections in man.

M. S. MARSHALL.

MORPHOGENESIS OF NEGRI BODIES. S. NICOLAU and L. KOPCIOWSKA, Ann. Inst. Pasteur **53**:418, 1934.

In a previous report (*Compt. rend. Soc. de biol.* **115**:262, 1934) the authors considered the dispersion of rabies virus in the nervous system. In the present report (figs. 1-22, colored) they consider the development of Negri bodies, typical on the seventh day, in the neurons of the spinal ganglions of rabbits inoculated in the sciatic nerve with street virus. The general morphogenesis is pictured as an orientation and flocculation of Nissl bodies. The authors picture the formation of Negri bodies as a defense reaction on the part of certain cells having exterior contacts; cells not so situated and functionally unable to cope with the virus develop no Negri bodies and are disintegrated.

M. S. MARSHALL.

INCLUSION BODIES IN YELLOW FEVER. S. NICOLAU, L. KOPCIOWSKA and M. MATHIS, Ann. Inst. Pasteur **53**:455, 1934.

Typical nuclear inclusion bodies were invariably noted in the neurons of the spinal ganglions of monkeys infected by cerebral, intraperitoneal or mosquito-bite injections. A majority of sections from the livers of twenty-two infected human beings also showed characteristic inclusions. In all mice as well as in guinea-pigs dying after subdural inoculation with the yellow fever virus the nerve cells of the neural axis contained inclusion bodies. These bodies were also found, more irregularly, in infected rabbits. The bodies appeared as oxyphilic corpuscles, sometimes surrounded by halos, from 1 to 3 or 4 microns in diameter, with no internal structure, in a rarefied karyoplasm which retained its normal tinctorial properties (color plate, 36 figs.).

M. S. MARSHALL.

TISSUE CULTURES IN TYPHUS FEVER. A. A. KRONTOWSKY ET AL., Ann. Inst. Pasteur **53**:654, 1934.

Successful efforts were made to grow two laboratory strains of the virus of typhus fever on living tissue. Leukocytes from healthy guinea-pigs were tried; also bits of Descemet's membrane from the eye, and a layer of cells from an exudate experimentally produced in the peritoneal cavity of a healthy guinea-pig. Inoculations were made with plasma of the blood of infected guinea-pigs, treated with heparin and rapidly centrifugated. The infective properties of culture originally too weak to infect were demonstrated.

M. S. MARSHALL.

THE PROBLEM OF THE BACTERIAL NUCLEUS. C. C. LINDEGREN, Zentralbl. f. Bakt. (Abt. 2) **92**:41, 1935.

Referring again to the various kinds of protoplasmic structures suggested as possible for bacteria, it is not possible to have a bacterial cell without a nucleus because that would mean that there were no genes. Life without genes is impossible. A diffuse nucleus is also impossible. The problem of the protoplasmic structure of bacteria therefore resolves itself into that of whether bacterial protoplasm is totally different from that present in any other kind of living form at present known or whether it is possible to demonstrate the presence of nuclear structure within it either by cytologic or by genetic technic.

FROM THE AUTHOR'S SUMMARY.

Immunology

HEMOLYTIC ANTIBODIES FOR SHEEP AND OX ERYTHROCYTES IN INFECTIOUS MONONUCLEOSIS. G. H. BAILEY and S. RAFFEL, J. Clin. Investigation **14**:228, 1935.

Bailey and Raffel found a marked increase of hemolysin for ox red blood cells in three cases of infectious mononucleosis in addition to a high titer of agglutinins and hemolysins for sheep red cells. The agglutinin for ox cells was distinctly elevated only in one of the cases, slightly in the second, and not at all in the third. The antibodies for the sheep as well as for the ox cells were easily removed by boiled and raw red blood cells of the sheep and ox, by those of the latter even more thoroughly than by those of the former. A large variety of other known carriers of the Forssman type of heterophilic antigens failed to absorb the antibodies from the serum of patients with infectious mononucleosis, with the exception of the kidney of the horse and of one strain of Clostridium Welchii. But even the latter two antigens did not absorb as regularly and as effectively as did the red cells of the sheep and of the ox. From that, the authors conclude that the antibodies in infectious mononucleosis are not heterophilic, or Forssman, antibodies. They suggest that after a determination of agglutinins for sheep red cells the serum be absorbed with ox red cells boiled. The removal of the antibodies for sheep red cells will indicate the presence of infectious mononucleosis. I. DAVIDSOHN.

THE RELATION BETWEEN THE TYPE SPECIFIC CARBOHYDRATES OF PNEUMOCOCCI AND THE BLOOD GROUP SPECIFIC SUBSTANCE. A. E. WITEBSKY, E. NETER and H. SOBOTKA, J. Exper. Med. **61**:703, 1935.

A relationship between the soluble specific substances of Pneumococcus and the blood group substance A of man can be demonstrated by the former's inhibition of sheep cell hemolysis by a group-specific A antiserum. However, there are quantitative differences between the various types. A striking difference exists between the acetyl and the deacetylated polysaccharide of Pneumococcus type I; the deacetylated carbohydrate fails to react with the group-specific A antiserum, while the acetyl carbohydrate shows a strong reactivity. The minimum amount of the acetyl polysaccharide which inhibits sheep cell hemolysis by A antiserum is almost as small as that of the group-specific carbohydrate isolated by Freudenberg and Eichel from urines of group A. The reactivity of the acetyl polysaccharide can be demonstrated not only by this inhibition of hemolysis test, but also by complement fixation and by inhibition of group-specific iso-agglutination. Fecal filtrates which possess the ability to destroy the blood group specific substances A and B of man also affect the acetyl polysaccharide of Pneumococcus type I. After incubation with an effective filtrate of feces the acetyl polysaccharide almost completely loses its potency toward the group-specific A antiserum and also its ability to inhibit the iso-agglutination of A blood cells. The acetyl polysaccharide of Pneumococcus type I that has lost its reactivity toward the group-specific A antiserum after treatment with a filtrate of feces still reacts with a type I pneumococcic antiserum that has been previously absorbed with the deacetylated polysaccharide of type I. Thus, the essential effect of a filtrate of feces on the acetyl polysaccharide of type I is not the cleavage of the acetyl group but some other chemical alteration. FROM THE AUTHORS' SUMMARY.

THERMOSTABILE BACTERICIDAL SUBSTANCE IN HUMAN SERUM. F. WULFF, J. Immunol. **27**:451, 1934.

A thermostabile bactericidal substance has been demonstrated to occur in human serum, especially during fever; its effect was particularly seen in tests with meningococci of a strain highly susceptible to the bactericidal substances of serum. The thermostabile bactericidal substance was found besides in a few other cases, namely, in tests with two other strains of meningococci, with three strains of

Pfeiffer bacilli, and with a strain of Diplococcus crassus—in this case in almost the same frequency as with the highly susceptible strain of meningococci. In tests with meningococci of the highly susceptible strain the thermostabile substance was demonstrable in 85 per cent of the febrile patients examined, one-fourth showing a marked action. The thermostabile substance could not be demonstrated in 90 per cent of the nonfebrile patients. Injection of sulphur in olive oil seems to stimulate the organism to produce a thermostabile bactericidal substance. An increase of the bactericidal substances in active serum was found in tests with a strain of Diplococcus, a phenomenon which is probably elicited only under quite special conditions. The thermostabile bactericidal substance seems to keep well in vitro. It possesses an enzyme property since it did not become fixed in absorption tests with the strain of meningococci which were killed by it.

FROM THE AUTHOR'S SUMMARY.

EXAMINATION OF THE BLOOD QUALITIES M AND N. H. ELBEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **24**:242, 1935.

One of the great difficulties connected with the preparation of anti-M and anti-N immune serums is the variability of the agglutinogens in the blood cells of different persons whose blood is employed for the absorption of anti-A and anti-B iso-agglutinins from the immune serums prepared in rabbits. Lattes suggested recently the use of boiled red blood cells. The cells are washed, and a fairly thin suspension is prepared and added drop by drop to a boiling physiologic solution of sodium chloride. Elbel tried the use of boiled red blood cells and found that while the agglutinogenic properties were considerably and regularly reduced the disadvantage was offset by a number of advantages: (*a*) A batch of blood with the same agglutinogenic properties can be kept for a long period; (*b*) the blood cells remaining from specimens used for the Wassermann test can be sterilized and used; (*c*) the absorbed serum is not discolored.

I. DAVIDSOHN.

HETEROPHILIC ANTIBODIES IN GLANDULAR FEVER (INFECTIOUS MONONUCLEOSIS). L. MEIJLER and R. J. SIEMELINK, Nederl. tijdschr. v. geneesk. **28**:1952, 1934.

The test for heterophilic antibodies described by Paul and Bunnell established the diagnosis of infectious mononucleosis in 5 cases. A sixth case, in which the titer was 1:16 (by the first method of Davidsohn) is included by Meijler and Siemelink, although they assume that, to be diagnostic, the titer has to be 1:32. The first case, in the early course, had to be differentiated from appendicitis and later from acute leukemia. A rash and hemorrhages in the skin were also notable features. Another case was marked by abdominal findings and diarrhea. The serums of 400 patients with various diseases were studied as controls. The highest titer was 1:8 if one excepts the titers of 4 patients who had received injections of horse serum and 2 patients (1 with jaundice and 1 with a subacute leukemic myelosis) whose elevated titers of heterophilic antibodies could not be explained.

I. DAVIDSOHN.

Tumors

CARCINOMATOUS ENDARTERITIS OF PULMONARY VESSELS RESULTING IN FAILURE OF RIGHT VENTRICLE. EDWARD B. GREENSPAN, Arch. Int. Med. **54**:625, 1934.

Four cases of carcinoma in the lymph vessels of the lung are reported, in three of which the condition was secondary to scirrhous carcinoma of the stomach, and in one, secondary to adenocarcinoma of the sigmoid. The four patients presented symptoms of cough, tachypnea and cyanosis with inconspicuous physical signs. The cases in which the involvement of the pulmonary lymph vessels was secondary to gastric carcinoma presented diffuse obliterative endarteritis of many

pulmonary arterioles and small arteries, due chiefly to the influence of the carcinomatous growth in the neighboring perivascular lymphatics, rarely to carcinomatous emboli. In two of the cases, failure of the right ventricle of the heart was the direct result of the diffuse obliterative changes in the pulmonary vessels. In cases of right ventricular cardiac failure presenting no significant pulmonary or cardiac findings, the possibility of a diffuse secondary carcinoma in the lymph vessels of the lungs with accompanying obliterative endarteritis should be considered.

FROM THE AUTHOR'S SUMMARY.

A VIRUS-INDUCED MAMMALIAN GROWTH WITH THE CHARACTERS OF A TUMOR (THE SHOPE RABBIT PAPILLOMA). P. ROUS and J. W. BEARD, J. Exper. Med. **60**:701, 723 and 741, 1934.

Growth on Implantation Within Favorable Hosts.—Rabbit papillomas developing on the skin as the result of virus inoculations can be readily transferred to the inner organs of favorable hosts by implanting bits of the living tissue. The growths thus produced proliferate actively, as a rule, and frequently cause death. Often they are markedly invasive and destructive, and they tend to recur after excision. Bacterial infection may greatly enhance their malignancy. Accidental dissemination may occur during operation, and distribution to the peritoneal surface has been repeatedly noted. There may be no cellular reaction about the invading epithelium of interior growths, but usually some new formation of connective tissue takes place, its amount varying inversely with the rate of epithelial proliferation. An immediate reason for the inflammatory changes and scarring found beneath long-established skin papillomas exists in the trauma and secondary infection to which the projecting, necrotizing masses have been subjected. In animals dying of progressively enlarging interior growths the skin papillomas may long have been stationary in size. The growths appearing after the transfer of papillomatous tissue to the inner organs are due to the survival and multiplication of the transplanted cells. However, the virus can be readily recovered from them, in the case of wild rabbits. No distinctive changes in the blood of the host have been found. The virus itself is highly specific for the epithelium of the skin, failing to act not only on that of the other organs thus far tested but even on embryonic skin. The papilloma frequently penetrates into the blood and lymph vessels, especially at the edge of an implantation growth. The intravascular injection of fragments of it sometimes results in pulmonary nodules of characteristic morphology. These are due to survival and proliferation of the injected cells. Secondary nodules have been encountered at autopsy in a lymph gland and in the lungs, but under conditions more suggestive of operative dissemination of the growth than of true metastasis. Implantation growths of the papilloma in favorable hosts have the morphology of epidermoid tumors of greater or less malignancy. They behave as these do and elicit similar changes in the surrounding tissue.

Experimental Alterations of the Growth on the Skin.—The injection of scarlet red into the skin about rabbit papillomas resulting from virus inoculations causes them to invade the underlying tissue and form large fleshy masses beneath the surface. Histologically these appear malignant, and they frequently invade the blood vessels. Covering young papillomas with a layer of collodion causes them to burrow downward, which results in discoid masses that enlarge progressively by expansive growth beneath the epidermis and by invasion. Such masses, like the nodules resulting from implantation, have the papillae turned toward their interior, the apparent reverse of what occurs when the growth is situated on the skin surface. The reasons for this are analyzed. The peculiarities of the host influence skin papillomas not a little, as is plain from the forms they assume; but the epithelial changes induced by the virus take a single direction, and no significant variations from type have been encountered. Local or generalized retrogression of the experimentally induced papilloma is not uncommon. The histologic alterations that take place are identical with those attending retrogression

of the epidermoid tumors, and the reactive changes taking place in the surrounding tissue are also like those about such tumors. The slowing and cessation of growth that occur secondarily in virus-induced skin papillomas are associated with the formation under them of a dense layer of connective tissue, and to this their behavior is attributable. Similar findings have often been recorded for tumors, notably for the epidermoid cancers produced in rabbits by tarring.

Further Characters of the Growth; General Discussion.—Experimental study of the rabbit papilloma of Shope, a growth caused by a virus, has shown that it possesses the immediate characters whereby tumors are recognized. Often it looks and acts like a malignant neoplasm. It differs from the tumors as a group, however, in its incidence, which is that of an infectious process, and from other mammalian tumors in that its cause has been demonstrated. The possible bearing of the findings on the problem of tumor causation is discussed. The morphology and behavior of the generality of tumors can no longer be taken to exclude the possibility that these are produced by extraneous, living entities. The incidence of some of the tumors, at least, and the failure to demonstrate their cause can both be explained on the assumption that they are due to such entities widely distributed in or on the animal population but effective only under special circumstances. Present knowledge makes this assumption reasonable as a basis for further work.

FROM THE AUTHORS' SUMMARIES.

GELATINOUS CARCINOMA OF THE BREAST. B. J. LEE, H. HAUSER and G. T. PACK, Surg., Gynec. & Obst. **59**:841, 1934.

Gelatinous (colloid) carcinoma occurs in many organs which normally secrete mucus. Of the cancers of the breast this form constitutes from 1 to 2 per cent. Two forms are recognized: (*a*) the primary gelatinous form in which the gelatinous features predominate and (*b*) ordinary carcinoma with secondary gelatinous degeneration. The latter may be termed myxoid or mucoid carcinoma depending on whether the gelatinous changes arise by metaplasia in the connective tissue or by secretion directly from the carcinoma cells. Of the two origins for the gelatinous material, the latter is the more common. This form of carcinoma is usually slower in growth than ordinary carcinoma, and one of the reasons is that the tumor often arises on the basis of a preexisting benign mammary adenoma. In the thirty cases studied no essential differences were observed in age, sex, race distribution, history of lactation and trauma between gelatinous carcinoma and ordinary carcinoma. Metastases occur comparatively late, are commonly confined to the axillary nodes and do not necessarily show gelatinous changes. The end-results of the writers' cases indicate an appreciably higher percentage of cures than with other forms of cancer of the breast.

FROM THE AUTHORS' SUMMARY (WARREN C. HUNTER).

EXPERIMENTAL BONE SARCOMA. A. BRUNSCHWIG and P. H. HARMON, Surg., Gynec. & Obst. **60**:30, 1935.

A transplantable rat sarcoma originating in the abdominal wall, the cells of which do not exhibit osteogenic properties, was inoculated into the medullary cavity and beneath the periosteum of long bones. The tumor penetrated the cortex, elevated the periosteum and caused it to lay down new bone in the form of radiating trabeculae within the tumor. Evidence is presented to show that all of the new bone in the tumor was periosteal in origin and not the result of osteoblastic properties acquired by the tumor cells from implantation within bone. In man elevation of the periosteum by osteogenic sarcoma may be an important contributing factor to the formation of new bone even though the tumor cells themselves have osteogenic properties. The mode of new bone formation in Ewing's sarcoma is quite analogous to that in the experimental tumors described here.

FROM THE AUTHORS' SUMMARY (WARREN C. HUNTER).

GROWTH-PROMOTING AND GROWTH-INHIBITING PROPERTIES IN BLOOD OF MICE RESISTANT TO A TAR-SARCOMA. F. C. PYBUS and E. W. MILLER, Brit. J. Exper. Path. **15**:207, 1934.

A difference has been found to exist between mice naturally immune to tar sarcoma NT_3 and mice resistant to this tumor as regards certain properties of their serum and plasma. When the immune mice have received three inoculations of NT_3 their serum and plasma do not inhibit the growth of this tumor in vitro but, on the contrary, definitely stimulate it; the serum and plasma of the resistant mice do not always have this stimulating effect but may occasionally inhibit the growth slightly. A similar difference has been found to exist between immune and resistant mice which have received eight inoculations each, but it is less definite than after three inoculations. The serum from resistant mice which have received three inoculations of NT_3 definitely stimulates the growth of c63 in vitro, and slightly stimulates the growth of normal mouse heart. The serum from immune mice which have received three inoculations does not affect the growth in vitro of normal mouse heart. No adverse effect on the growth of NT_3 in vitro is shown by the serum or plasma of mice which have once been inoculated with NT_3 and in which the tumors are actively growing, or are regressing, or have completely regressed. In the first two cases growth is, if anything, slightly stimulated. Certain objections to the present method of investigation are discussed, and comparisons are drawn between conditions in vivo and in vitro.

FROM THE AUTHORS' SUMMARY.

INJURY IN THE GENESIS OF TUMOURS OF THE GONADS. R. A. WILLIS, Brit. J. Exper. Path. **15**:234, 1934.

In the experiments recorded, 107 rats (82 males and 25 females) were used. In the different groups the animals were of different ages from 2 months up to middle adult age. The testes and ovaries were subjected to a great variety of traumatic and chemical injuries, and the animals were kept for from twenty-five to thirty-five weeks thereafter. The changes observed in the damaged organs were those of necrosis and its sequelae; no tumors appeared. These experiments, then, so far as they go, afford no evidence that local injury is capable of evoking neoplasia in gonadal tissue. While a larger series of experiments on a variety of mammals is desirable, the result obtained in this investigation at least serves to strengthen the suspicion that injury and inflammatory processes play no more than a coincidental part in the histories of testicular or ovarian tumors.

FROM THE AUTHOR'S SUMMARY.

CANCER OF SKIN AND INCREASE IN INCIDENCE OF PRIMARY TUMOURS OF LUNG IN MICE EXPOSED TO DUST OBTAINED FROM TARRED ROADS. J. A. CAMPBELL, Brit. J. Exper. Path. **15**:287, 1934.

Mice were repeatedly exposed to dust containing about 2 per cent tar obtained by sweepings from tarred roads. Cancer of the skin developed in 70 per cent of those surviving long enough. The incidence of primary adenoma of the lung was increased to ten times that of the controls; the lungs of the dusted mice contained much dust. The breathing of carbon monoxide, if anything, retarded the effects of dusting. The bearing of this research on the debated increase in tumors of the human lung cannot be assessed at present. . The mice were exposed to much more excessive dusting than occurs with man. Cleanliness prevents cancer of the skin in man, and the natural mechanism for removal of dusts from the healthy lung may suffice for the small amounts of dust inhaled. There is the further question whether these tumors of mice may be compared with those of the human lung. The experiment with mice is to be repeated, and attempts will be made to transplant some of the tumors; the effects of dust, with the tar products removed, will also be studied.

FROM THE AUTHOR'S SUMMARY.

THE PRODUCTION OF TUMOURS IN FOWL WITH A COLLOIDAL SOLUTION OF 1:2:5:6-DIBENZANTHRACENE. I. BERENBLUM and L. P. KENDAL, Brit. J. Exper. Path. **15**:366, 1934.

Repeated injections of a 0.007 per cent colloidal solution of dibenzanthracene in water into the breast muscle led to the production of spindle-cell sarcoma in eight of twelve birds which survived more than twelve weeks. The total amount of dibenzanthracene injected was about 1.8 mg. Secondary deposits were found in three birds. Five of these tumors were transplanted into other birds, and two of them grew successfully. In one of these inoculated birds metastases were present in the lungs. The administration of kieselguhr together with colloidal dibenzanthracene did not appear to influence significantly the development of the tumors. Eighteen months after intramuscular injections of 0.6 mg. of dibenzanthracene, none of the substance could be detected in the muscle about the site of injection.

AUTHORS' SUMMARY.

THE STRUCTURE OF TERATOMA. R. A. WILLIS, J. Path. & Bact. **40**:1, 1935.

Fourteen teratomas have been studied and mapped in serial slabs and the distribution and relationships of the component tissues have been worked out. In the identification of many of the tissues difficulties are encountered. An intimate knowledge of the histology of adult and embryonic tissues is necessary. Immature glandular and neuro-epithelial tissues are readily confused with one another. For the clear delineation of neuroglial tissue and especially for the identification of immature neuroglial cells Cajal's gold method is desirable. Unless accompanied by hair follicles or cutaneous glands, stratified squamous epithelium cannot be identified as epidermal, since squamous metaplasia frequently occurs in the glandular components of teratoma. Renal tissue is a rare component, in the identification of which special caution is essential; it may be immature even in an otherwise fully differentiated growth. Function in teratomatous tissues—secretion, hematopoiesis, movement, nervous activity—is of interest in connection with the problems of the prefunctional and functional differentiation of tissues. Teratomas of the testis are almost always malignant, and with rare exceptions the malignancy involves many or all of the component tissues, though perhaps in different degrees. Most teratomas exhibit no signs of somatic axiation, segmentation or delamination of germ layers; they possess no organs or true somatic regions; they exhibit anomalous excess of some components and anomalous absence of others, and they exhibit abnormal mixtures and relationships of tissues and coexistence of tissues of widely different degrees of maturity. For these reasons, the view that a teratoma is homologous with a fetus must be rejected; this means rejection of the hypotheses that the teratoma represents a twin inclusion and that it represents parthenogenesis. It is noteworthy that on incomplete examination a teratoma may present a spurious resemblance to a fetus. Tissue correlations, probably similar to those obtaining in normal ontogeny, are evident in teratomas. Various growing epithelia appear to induce specific changes in associated plastic mesenchyme; certain glandular epithelia evoke the formation of smooth muscle; young central nervous tissue evokes chondrification; tooth development exhibits its characteristic and complex tissue correlations; respiratory mucosa induces the formation of cartilage, nervous tissue the formation of a meninx-like sheath or of nerve-sheath elements, epidermis the formation of dermis and certain mucosal epithelia the formation of lymphoid tissue. Tertoma constitutes a field of study in which pathologist and embryologist have a common interest and can mutually benefit each other.

FROM THE AUTHOR'S SUMMARY.

LEUKEMIA TRANSMISSIBLE BY A SPINDLE-CELL SARCOMA IN THE MOUSE. L. D. PARSONS, J. Path. & Bact. **40**:45, 1935.

A leukemic condition in mice coincident with and transmissible by the grafting of a spindle-cell sarcoma is described. Examination of the cells of the blood of the affected animals shows the leukemia to be myeloid, with large numbers of

pathologic polymorphonuclears. The hemohistioblast, also present in the blood stream in this condition, is suggested as the primitive cell giving rise directly to pathologic polymorphonuclears of the granular series. The activity of the fixed cells of the spleen, liver and other organs appears to be responsible for the gradual appearance and rise in number of primitive cells in the blood stream.

FROM THE AUTHOR'S SUMMARY.

CARCINOMA OF THE INTESTINE IN RATS. R. A. WILLIS, J. Path. & Bact. **40**:187, 1935.

The appearance of two almost identical carcinomas in two closely related young rats of the same age gives food for thought. Suppose that the experiments performed on these rats had been dietetic, say the administration of some carcinogenic substance with the food. Very erroneous conclusions could easily have been reached. This report clearly emphasizes the need for great caution in making deductions concerning the incidence or the genesis of neoplasms in experimental animals, unless adequate numbers and full controls are used.

FROM THE AUTHOR'S COMMENT.

THE ACTION OF RADIUM ON THE INORGANIC STRUCTURE OF TUMOUR CELLS AS SHOWN BY MICROINCINERATION. E. S. HORNING, Scient. Rep. Invest. Imp. Cancer Research Fund **11**:67, 1934.

The inorganic structure of the cells of adenocarcinoma *27* following microincineration is briefly described and compared in detail with that in similar incinerated sections of the tumor irradiated and examined after periods ranging from six hours to twenty-four days. An increased cytoplasmic ash is recorded in the tumor cells from six to eight hours after irradiation, which at this phase is apparently not the result of immediate degenerative changes. This phenomenon is maintained in the cytoplasm twenty-four hours after irradiation, and is accompanied by cellular hypertrophy, which is more marked on the third day. The maximum increase of mineral salts occurs on the sixth day following irradiation, at which time degenerative areas are found in all tumor cell masses. These phenomena may be partly due to the secondary effect of irradiation on the vascular supply. The degeneration may be followed clearly in the inorganic residues of the tumor cells owing to the absence of ash in the fat globules which collect in the cytoplasm. The hypertrophied nucleoli and increased chromatin masses are clearly recognizable in the ash. The multinucleate cell formation and final disintegration stages in the tumor cells also involve characteristic alterations in the inorganic material.

FROM THE AUTHOR'S SUMMARY.

THE ACTION OF RADIUM ON CANCER CELLS. H. G. CRABTREE and W. CRAMER, Scient. Rep. Invest. Imp. Cancer Research Fund **11**:75, 89 and 103, 1934.

Effects of Hydrocyanic Acid, Iodo-Acetic Acid and Sodium Fluoride on the Metabolism and Transplantability of Cancer Cells.—Hydrocyanic acid produces primarily an inhibition of respiration which is of the order of from 85 to 95 per cent in concentrations of from one-thousandth to five-hundredth molar. As a secondary effect of this inhibition the aerobic glycolysis of tumor tissue increases to a value approaching that of anaerobic glycolysis. The effect of hydrocyanic acid is completely reversible in all concentrations up to twentieth molar. The primary effect of sodium fluoride and iodo-acetic acid is an inhibition of aerobic glycolysis, which increases progressively with increasing concentration. This direct checking of aerobic glycolysis is accompanied by a small indirect inhibition of respiration which increases with the time of exposure. Within certain characteristic concentrations these inhibitions are reversible after an experimental period of one hour. If these limits of concentration are exceeded, these two substances produce an irreversible damage in tumor cells. This damaging action appears even with

concentrations which are insufficient to effect a complete or almost complete inhibition of glycolysis. There is a close parallelism between the degree of metabolic recovery and the effect on the viability of the cell as measured by subsequent transplantations.

Some Factors Determining the Susceptibility of Cancer Cells to Radium.—It is possible to produce experimentally great variations in the susceptibility of cancer cells to radium by acting on the respiratory mechanism of the cell. It is not possible to do so by acting on the glycolytic mechanism. The measures used for action on the respiratory mechanism were anaerobiosis, subjection to hydrocyanic acid and subjection to cold. Although all three have the same general action of diminishing the functional activity of the respiratory mechanism, their effects on the susceptibility to radium are in opposite directions. Anaerobiosis diminishes, hydrocyanic acid and cold increase the susceptibility to radium.

Factors Determining the Susceptibility of Cancer Cells to Gamma Radiation.—Pure gamma rays have the same biologic effect on cancer cells in vitro as a mixture of beta and gamma rays. In both cases the functional condition of the respiratory system determines the biologic response of the cell, while the glycolytic mechanism is not primarily concerned. FROM THE AUTHORS' SUMMARIES.

VARIATIONS OF METABOLISM AND RADIO-SENSITIVITY OF TISSUES IN BICARBONATE- AND PHOSPHATE-BUFFERED MEDIA. H. G. CRABTREE, Scient. Rep. Invest. Imp. Cancer Research Fund **11**:119, 1934.

A comparison has been made of the carbohydrate metabolism exhibited in vitro by tissues suspended in saline mediums buffered with phosphate and bicarbonate, respectively. The respiration of rat liver and Jensen's rat sarcoma was well maintained during four hours in both mediums, but the values found in phosphate-Ringer solution were consistently from 20 to 30 per cent lower than those in bicarbonate-Ringer solution. The susceptibility of tumor tissues to gamma radiation has been shown to be a function of the condition of the respiratory system. When tumor slices are suspended in bicarbonate-buffered and phosphate-buffered mediums, respectively, treated with gamma radiation and subsequently transplanted, the damaging influence of phosphate-Ringer solution is made apparent by the lower number of "takes" or the subsequent slower rate of growth of the transplants. This indirect method of showing the adverse effect of phosphate-Ringer solution confirms the results obtained by direct measurement of carbohydrate metabolism. Phosphate-Ringer solution, in some unknown manner, damages the respiratory system of tumor tissues. FROM THE AUTHOR'S SUMMARY.

THE THERAPEUTIC ACTION OF RADIUM ON SPONTANEOUS MAMMARY CARCINOMA OF THE MOUSE. W. CRAMER, Scient. Rep. Invest. Imp. Cancer Research Fund **11**:127, 1934.

The spontaneous mammary carcinomas of the mouse show differences in sensitivity to radium. They present, therefore, a suitable material for the study of the factors which determine the radiosensitivity and radioresistance of malignant new growths. With a given dose which in the radiosensitive tumor produces rapid regression, the radioresistant tumor shows only an arrest of growth or a partial regression. In both cases the action is only a local one and is restricted to the irradiated area. With the doses given, no evidence has been obtained of a stimulation of growth or of an enhanced metastatic dissemination. The process of regression in the radiosensitive tumors corresponds closely to that described for a radiosensitive transplantable tumor of the mouse. Histologically it begins with an invasion of the tumor by macrophages. This leads to the formation of a massive stroma overgrowing the tumor and splitting the malignant parenchyma into narrow strands of living and viable cells. It is pointed out that, although

histologically these irradiated viable cells appear normal, they have undergone a change so far as they have been temporarily deprived of their power of growth. The process of regression as a whole is, as previously shown, not due to a direct lethal action on the cancer cells nor entirely to an action on the tumor bed, but is the result of a damage inflicted on both the tumor parenchyma and the tumor bed, followed by repair. In the radioresistant tumors irradiation does not produce a macrophage invasion and a subsequent overgrowth of the stroma. It is shown experimentally that the temporary loss of growth which malignant cells undergo after irradiation is due to a direct action on these cells. They may remain in this dormant condition over a relatively long period, but eventually they recover from it and resume their usual rate of growth. The bearing of this phenomenon on the clinical results of radiotherapy is discussed, and a distinction is drawn between the true recurrences due to this condition and the apparent recurrences which are really the result of a new development of malignancy due to an insufficiently extensive irradiation. The fact that it is possible to bring about locally the disappearance of a malignant new growth by an agent which does not kill all the malignant cells directly, but only inflicts on them a temporary damage of a specific nature, indicates the possibility of a systemic therapy of cancer along the same lines.

FROM THE AUTHOR'S SUMMARY.

Technical

"SPOT" PREPARATIONS IN THE POSTMORTEM DIAGNOSIS OF HEMATOPOIETIC DISEASES. A. F. ZANATY, Virchows Arch. f. path. Anat. **293**:335, 1934.

"Spot" preparations made at the time of autopsy from the various organs and tissues are highly recommended as an aid in the diagnosis of diseases of the hematopoietic organs. They may be stained by a variety of methods and yield more satisfactory results than smear or "thick drop" preparations. O. T. SCHULTZ.

HISTOLOGIC DEMONSTRATION OF GLYCOGEN IN MUSCLE. A. NOLL, Virchows Arch. f. path. Anat. **293**:409, 1935.

Pieces of fresh muscle from 0.5 to 1 cm. long and a few millimeters wide are placed in 5 per cent aqueous potassium hydroxide at room temperature for a maximum of four hours. The tissue is then washed in water for one minute. It is then placed in 96 per cent alcohol, which is changed several times during the first few hours, followed by immersion in absolute alcohol, in which it remains for at least twenty-four hours. It is embedded in pyroxylin (celloidin). The sections may be stained by Best's carmine method or with iodine. O. T. SCHULTZ.

PRESERVATION OF SHEEP ERYTHROCYTES FOR COMPLEMENT FIXATION. S. GINSBURG and R. SELIKOWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:157, 1934.

The sheep blood was defibrinated and washed twice with a modified Ringer-Locke solution (the dextrose is left out and boric acid crystals are added in the concentration of 1 per cent). The cells are suspended in the same solution in the proportion of 1:33. The red cells remained satisfactory for hemolytic and complement-fixation tests for from ten to twenty days; their fragility remained unchanged for a similar period. The modified Ringer-Locke solution (without the boric acid) is sterilized in the Arnold sterilizer for thirty minutes. A precipitate forms during sterilization which has no harmful effect. The boric acid crystals are now added. The solution keeps well for from one to two months at room temperature.

I. DAVIDSOHN.

FLOCCULATION TEST FOR SYPHILIS WITH THE ANTIGEN ABF (ANTIGÈNE-BRUXELLES-FLOCULATION). M. STERN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:228, 1934.

The technic of the preparation of the antigen, which was originally suggested by Bordet, is not given. The method of its dilution and the technic of the test are described and impress one by their simplicity. The results were compared with those of the Wassermann test (Wadsworth antigen), the micro test, the clearing test of Meinicke and the Kahn test. The test proved highly specific with comparatively few false reactions. The antigen can be used for the test with cerebrospinal fluid, but a large amount of the fluid is needed. I. DAVIDSOHN.

PRESERVATION OF COMPLEMENT. H. MIRDAMADI and K. GIESE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **83**:304, 1934.

Complement was diluted with an equal volume of a 12 per cent solution of sodium acetate containing 4 per cent boric acid. The serum of the guinea-pigs which contained normal antisheep lysin was eliminated. The preserved complement kept well for a number of weeks. I. DAVIDSOHN.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 28, 1935

WILLIAM C. VON GLAHN, *President, in the Chair*

IRVING GRAEF, *Secretary*

ABSCESS OF THE LIVER DUE TO FRIEDLÄNDER'S BACILLUS. CHARLES T. OLCOTT.

The literature concerning abscesses of the liver caused by Friedländer's bacillus has been reviewed. Five cases have been found in which there were pulmonic and hepatic lesions, and five others in which the lungs were not involved (Gilbert-Dreyfuss and Dausse, C.: *Rev. méd.-chir. d. mal. du foie* **4**:481, 1929 [references]. Lutembacher, R., and Debains: *Ann. de méd.* **8**:460, 1920. Le Sourd and Draillard: *Gaz. d. hôp.* **105**:1185, 1932). In the latter group the kidney was also involved three times, the meninges and spleen each twice and the gallbladder once.

The case presented was that of a woman 51 years of age on the service of Dr. E. F. DuBois, New York Hospital. She had had diabetes mellitus for eleven years and infection of one foot necessitating amputation three years before admission to the hospital. She had had a nonproductive cough and repeated vomiting on admission. The abdomen was diffusely tender, especially in the right upper quadrant, and there was a palpable mass extending 8 cm. below the costal border. The heart was enlarged, and there were some râles in the chest. Blood cultures showed Friedländer's bacillus. The white blood counts showed 44,000 and 23,200 white cells with 90 per cent polymorphonuclears, two-thirds immature forms. The patient died two days after admission.

At autopsy (Henry S. Dunning) there was advanced arteriosclerosis with fibrosis of the pancreas. The heart was dilated and hypertrophied. The lungs showed congestion and edema but no pneumonia. The serous cavities were clear. The liver weighed 2,800 Gm., and there was a multilocular abscess cavity 11 cm. across in the right lobe. This contained thick yellow liquid. The edges were irregularly trabeculated and white. There was surrounding congestion. Microscopically, polymorphonuclear cells were found in the central necrotic area. These were surrounded by mononuclear cells and fibroblasts. The spleen was soft and enlarged, and it showed infarcts, one of which was filled with pus.

Smears from the liver and spleen showed gram-negative encapsulated bacilli. Cultures from the cardiac blood, spleen and liver showed Friedländer's bacillus.

ATROPHY OF THE CORTEX OF THE ADRENAL GLAND WITH ADDISON'S DISEASE. JAMES A. MOORE (by invitation).

A 26 year old white married woman was admitted to the New York Hospital because of general weakness and fatigue of two months' duration. The family and past histories were essentially negative. For the past two months prior to her entry into the hospital there were increasing weakness and fatigue, loss of weight, nausea, vomiting and increasing brownish pigmentation of the skin.

Physical examination showed moderate dehydration, apparent loss of weight and increased brownish pigmentation of the skin over the flanks, abdomen, arm pits, nipples and buccal mucosa. The apex impulse was weak and diffuse but within the normal boundaries. The blood pressure was 74 systolic and 46 diastolic. The urine was essentially normal. The red blood cell count and the hemoglobin con-

tent were normal. The white blood cell count was 15,400, with 54 per cent polymorphonuclear leukocytes. The Kline test was negative. The urea nitrogen was 44 mg. per hundred cubic centimeters of blood, and the plasma chlorides 600 mg. The patient declined steadily and died three days after admission without apparent response to the administration of large amounts of sodium chloride by vein or to the intravenous use of 20 cc. of extract of adrenal cortex.

The essential features of the autopsy (Henry S. Dunning) were as follows: The skin and buccal mucosa were pigmented light brown, as described. The heart weighed 205 Gm. The circumference of the abdominal portion of the aorta was 2.5 cm. The coronary, splenic and renal arteries had unusually thin walls. There was a small partially calcified fibrocaseous nodule in the upper lobe of the right lung with a similar nodule in the tracheobronchial lymph nodes draining that area. The thymus gland weighed 7.5 Gm. and was grossly normal. Grossly the thyroid gland, pituitary gland, liver, pancreas, biliary tract and spleen were not remarkable. The right adrenal gland was gray-brown, homogeneous, soft and friable. It measured 2.5 cm. in length, 2 cm. in width and 0.3 cm. in thickness, with no differentiation into cortex and medulla. The left adrenal gland measured 4.5 cm. in length, 1.9 cm. in width and 7 mm. in thickness, with definite differentiation into cortex and medulla. The cortex was gray-brown, homogeneous, fairly firm, with a slightly lobulated surface, and measured 0.5 mm. in thickness. The medulla was gray, soft and friable. At the lower pole of this gland there was a small subcapsular hemorrhage. The kidneys showed some brown pigmentation of the pyramids. The ureters, bladder and genital organs were normal.

On microscopic examination the basal cells of the pigmented skin and buccal mucosa were filled with fine brown pigment granules. The rectus muscle fibers showed some Zenker's hyaline degeneration. The thymus gland was not remarkable. The thyroid gland showed diffuse infiltration with lymphocytes and plasma cells, and the acini were lined by unusually tall epithelial cells and for the most part were devoid of colloid. The pituitary gland was normal. The capsule of the left adrenal gland was of normal thickness. The area between the medulla and the capsule was much reduced and showed only a few isolated islands of what appeared to be cortical cells with irregular outline, pink-staining cytoplasm and hyperchromatic vesicular nuclei, surrounded by congested capillaries, remaining stroma and a dense lymphoid infiltration. The medulla showed considerable lymphoid infiltration with some degeneration of the chromaffin cells in these areas. A section from the lower part of the right adrenal gland consisted entirely of well preserved medullary tissue with a few focal accumulations of lymphocytes. This section showed neither cortex nor capsule. Stains for acid-fast bacilli were negative.

This case conforms closely with those reported by Brenner and others. Both adrenal glands showed advanced atrophy of the cortex. The medulla in each instance was essentially normal in appearance except for the lymphoid infiltration. There were associated changes in the thyroid gland and rectus muscle fibers similar to those described in other case reports.

DISCUSSION

WILLIAM C. VON GLAHN: Since 1926 my associates and I have had five cases of Addison's disease following atrophy of the adrenal whereas in the past twenty-four years only six cases due to tuberculosis of the adrenal were observed. I am wondering if this is the experience of other pathologists?

ALFRED PLAUT: In the last five years I have seen two cases of Addison's disease, one associated with tuberculosis and one with atrophy.

ROBERT A. MOORE: It seems to me that cases of this type present certain problems and also certain opportunities for the study of the physiology of the adrenals. At New York Hospital in the past two years we have had two cases of Addison's disease; one was tuberculous and the other was this case of atrophy. I do not know what the relative importance of these associated conditions is, but

in the large series of 500 cases it is probable that a true index of the relative amount of atrophy is given, namely, 10 per cent. There is some indication, as Wells has pointed out in reviewing his cases, that this type of change is not dissimilar from acute yellow atrophy in which there is a profound degeneration of the parenchyma without fibroblastic proliferation.

One other point in connection with the morphology of the disease: The thymus was not enlarged, but certainly there were hypoplastic changes in the vessels of this patient. There was lymphoid infiltration in the thyroid, and the lymphatic tissue in the body was increased over that which would be expected in a person of this age. That brings up again the possible relationship of the adrenal to the so-called status thymicolymphaticus.

OSTEOID OSTEOMA. HENRY L. JAFFE.

(Material was presented on a bone lesion designated "osteoid osteoma.") Osteoid osteoma appears to be a distinctive benign bone tumor. It arises from osteoblasts. Irregularly between the osteoblasts intercellular material develops. In this way patches of osteoid tissue are formed. In the further progress of the lesion the osteoid becomes calcified and even converted into atypical bone. In the course of the conversion osteoclasts appear. Sometimes the lesions are rather vascular.

Osteoid osteoma is by no means a rare condition. Seven instances have been noted and studied in the laboratory during eighteen months. Nevertheless, this lesion has been mentioned in the literature only three times and has never before been interpreted as a distinctive bone tumor. Heine, in 1927, described one instance of the lesion under the title "A Bone Sequestrum in Process of Being Reincorporated into the Basal Phalanx of the Ring Finger." Hitzrot, in 1929, under the title "Sclerosing Osteomyelitis of the Carpal Scaphoid," presented before the New York Surgical Society a case the roentgenogram of which published in the transactions of the society closely resembles the roentgenogram in some of our cases. Bergstrand, in 1930, under the title "A Peculiar and Probably Not Hitherto Described Osteoblastic Disease in the Long Bones of the Hand and Foot," reported two cases that seem quite clearly to be instances of what I have called osteoid osteoma. He was at a loss to classify the condition but held that it was neither a tumor nor an inflammatory process, regarding it as a reactivation of an embryonal rest.

All the cases which I have observed had the following features in common: The patients were adolescents or young adults. The principal complaint was local pain. Uniformly the lesion originated in spongy bone areas. As observed roentgenographically the pathologic areas were roundish and clearly circumscribed. The lesions were small and closely similar in size. In every case operation was performed on the assumption that the lesion was an inflammatory one. Complete eradication resulted in the eventual disappearance of all symptoms without recurrence of the local condition.

It was indicated that osteoid osteoma is possibly related to the metacarpal bone tumor previously described by Dr. Mayer and Dr. Jaffe under the title "An Osteoblastic, Osteoid-Tissue-Forming Tumor of a Metacarpal Bone." This metacarpal bone tumor is possibly an osteoid osteoma which, because of incomplete removal, continued to proliferate and began to take on the characteristics of osteogenic sarcoma.

As to differential diagnosis, osteoid osteoma has no features suggesting that it has an inflammatory origin or an origin from an embryonic rest, or that it represents an unfamiliar healing stage of a giant cell tumor, localized osteitis fibrosa or cyst. Altogether, it seems fair to assume that osteoid osteoma is a distinctive benign osteoblastic bone tumor which has hitherto been overlooked as such, and the true incidence of which is still to be determined.

It is suggested that osteoid osteoma is possibly the benign counterpart of malignant osteogenic sarcoma.

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HISTOGENESIS OF LYMPHOSARCOMATOSIS. J. C. EHRLICH (by invitation) and I. E. GERBER.

Histologic studies of the biopsy and necropsy material from eighteen cases of lymphosarcomatosis revealed varied histologic pictures which could be grouped into three main types on the basis of the morphologic characteristics of the predominating cell in each case. There were found, first, cases in which large pale cells in either symplasmic or reticular arrangement predominated. Then there was a group in which the lymphosarcomatous tissues were composed of mixed cells, partly reticular, as in the former group, and partly free. The morphology of these free cells resembled that of immature large lymphocytic cells. Finally, there were encountered cases in which the lymphosarcomatous tissues were composed predominantly of free cells, whether of the immature or of the mature lymphocytic type. These three types were termed, for descriptive purposes, "reticular," "intermediate" and "lymphocytic," respectively.

These types were found to correspond in their essential morphologic features to the immature, intermediate and mature cells resulting from normal differentiation of the cytoplasmic reticulum along lymphopoietic lines. This similarity, together with evidences of the progressive transformation of the less mature into the more mature cell types in lymphosarcomatosis, indicated that the histogenesis of this disease consists of progressive lymphopoietic differentiation of the cytoplasmic reticulum. This process is confined chiefly to the cytoplasmic reticulum of lymphatic tissue, viz., lymph nodes, gastro-intestinal tract, etc.

Lymphopoiesis as it occurs in lymphosarcomatosis manifests blastomatous characteristics. These are indicated by the aggressiveness of the tumor masses and the atypical character of the cells.

Lymphosarcomatosis arises in a region of lymph nodes, from which it extends to other regions of lymphatic tissue and other organs in progressive fashion. This spread occurs by direct local extension and by metastasis via the lymphatics and the blood stream. In addition, there occurs autochthonous formation of lymphosarcomatous foci in many centers of lymphatic tissue. This autochthonous origin is evident in partially involved nodes, where intermediate stages in the formation of these foci from local reticulum cells may be observed, and in the diffuse involvement of the malpighian follicles of the spleen in two of our cases.

As a result of these modes of spread many cases of lymphosarcomatosis show, in their late stages, a widespread involvement of the lymphatic tissues (with the exception of the spleen) and of other organs.

The origin of lymphosarcomatosis simultaneously in various lymph nodes in one region, the autochthonous mode of spread and the tendency toward restriction to one type of tissue separate this disease from true sarcoma. Lymphosarcomatosis bears certain resemblances to lymphadenosis, such as identical histogenesis, restriction to lymphatic tissue and systematization. Nevertheless, the focal origin of the former, the more aggressive character of its growth, the focal involvement of lymph nodes and the limited systematization serve to characterize it as a blastomatous disease of lymphatic tissue in contrast to the hyperplastic character of lymphadenosis.

From an oncologic point of view lymphosarcomatosis may be classified as a blastomatous disease in the group of hemoblastoses.

DISCUSSION

HENRY S. DUNNING: I should like to ask two questions: first, what part the histiocyte plays in these tumors, if any, and second, whether Dr. Ehrlich believes that the histiocyte is also formed by a reticulum cell.

J. C. EHRLICH: In answer to the first question, what part does the histiocyte play, we have taken special note of cells which could be recognized as histiocytes in lymphosarcomatous tissue because of included phagocytosed material, and there was no instance in which such cells, whether they were in the follicles or in the pulp or in the marginal sinuses of the lymph node, appeared to play any part whatever. There were numerous cases in which the lymphosarcomatous tissue appeared punctured by large pale histiocytes which showed no evidence of participation in the formation of lymphosarcoma cells.

In answer to the second question, histiocytes are considered a part of the reticulo-endothelial system. If you want to ask, "Are these histiocytes formed by reticulum cells?" I should say, "Yes, I believe they are, but most frequently they are derived from the littoral cells or the endothelial part of the reticulo-endothelial system."

VISCERAL NEUROGENIC SARCOMATOSIS. SEATON SAILER.

A rapidly fatal tumor in a woman 54 years of age, arising in the root of the mesentery and involving the visceral and parietal peritoneum and pleura, is reported.

DISCUSSION

NATHAN CHANDLER FOOT: It seems to me very important in the study of these tumors to distinguish between those of Schwann cell origin and those of fibroblastic origin, and I think that one of the chief obstacles to making this distinction has been the disinclination of pathologists to get away from the old tried and true hematoxylin-eosin stain. It is important to use a trichrome stain such as Dr. Sailer used to differentiate roughly between the fibrous tumors and the nerve sheath tumors, the tumors of the sheath of Schwann. It seems quite possible that if one used a little more complicated staining technic one would be able to find out the histogenetic origin of these tumors and to distinguish between those which come from the perineural fibrous tissue and those which come from the sheath of Schwann, as this one apparently did. One has, on one hand, a slow-growing group of singly occurring tumors which, if they are not completely extirpated, are apt to recur and with each recurrence become more malignant until they are finally sarcomas. The question arises whether they are related to the multiple tumors Dr. Sailer has just described, on the other hand. It is quite possible that both camps may be right; that is, that Penfield's contention that neurogenic sarcoma is of fibrous origin and the contention of the French school that it is of Schwann cell origin may both be right under certain circumstances, and that by using more careful staining technic it will be possible to find out which tumors have their origin in Schwann's sheath and are therefore really neurogenic, and which are merely fibrosarcomas occurring along the course of nerves.

SHELDON A. JACOBSON: Some time ago at the Hospital for Joint Diseases we had a tumor in which the following observations were made: The main tumor was a mass which occupied a completely destroyed lower dorsal vertebra and extended also into the vertebrae above and below. There was a marked compression of the spinal cord which had given rise to symptoms of transverse myelitis. The ileum was the site of some polypoid nodules on narrow peduncles, the largest of which was about the size of a plum. In the mediastinum was a rather large nodule which was poorly demarcated, infiltrating the wall of the aorta and completely penetrating that organ to be seen lying as naked tumor material within the lumen. On microscopic section the tumor presented an appearance very similar to that in the photomicrographs shown by Dr. Sailer. We made a final anatomic diagnosis of schwannoma in the sense used by Masson, and let it go at that.

Regular Meeting, March 28, 1935

WILLIAM C. VON GLAHN, *President, in the Chair*

IRVING GRAEF, *Secretary*

A CASE OF THROMBOLYMPHANGITIS OF THE THORACIC DUCT ASSOCIATED WITH ABDOMINAL SYMPTOMS NECESSITATING EXPLORATORY LAPAROTOMY. S. H. POLAYES.

A Puerto Rican, 55 years of age, was seized with persistent abdominal pain which radiated from the umbilical region to the rest of the abdomen. Several years previously he had had epididymitis, which lasted several months, and for the past three months he had been having vague abdominal pains.

On admission to the hospital the provisional diagnosis was ileitis (influenza) and acute pancreatitis. An exploratory laparotomy failed to reveal more than marked congestion of the terminal ileum. The postoperative reaction was poor, and the patient died on the third day after admission, following a sudden rise in temperature from 99 to 105.5 F.

The blood on admission showed 13,800 leukocytes, of which 88 per cent were polymorphonuclear cells and 12 per cent were lymphocytes. Twelve hours later the leukocyte count dropped to 5,850, of which 94 per cent were polymorphonuclears.

The chemical findings in the blood were normal.

Urinalysis showed numerous red cells and a trace of albumin.

Postmortem examination showed that the most important abnormalities were confined to the genital and lymphatic systems. The epididymis was the seat of chronic inflammation, which was complicated by thrombophlebitis of the pampiniform plexus. The surrounding lymphatics were apparently involved, as evidenced by marked acute lymphadenitis of the lateral and preaortic lymph nodes. The cisterna chyli was filled with purulent exudate, which extended all along the thoracic duct, presenting a marked but nonoccluding thrombolymphangitis of the duct extending to its termination in the neck, where it was lost in a mass of suppurative lymph nodes. The purulent process spread from the duct to the mediastinum and pleura, both of which were the seat of a purulent exudate. Streptococcus haemolyticus was recovered in pure culture from the contents of the duct as well as from all the other purulent areas and from the pampiniform plexus.

The final anatomic diagnoses were as follows: chronic epididymitis; suppurative thrombophlebitis of the pampiniform plexus; acute suppurative lymphadenitis (lumbar, thoracic, mediastinal and cervical); suppurative thrombolymphangitis of the thoracic duct; suppurative mediastinitis and pleuritis; confluent lobular pneumonia and old apical tuberculosis; a laparotomy wound with local peritonitis; cortical cysts of the kidney (arteriosclerotic); diverticulum of the duodenum.

The review of the literature reveals the rarity of the condition. Pappenheimer referred to a total of ten cases reported in the English, French and German literature up to 1921. Von Glahn in a similar review in 1924 described a case of his and called attention to a case reported by Warthin and another by DeForest, both of which, he stated, were omitted from Pappenheimer's collection. Kryloff, as well as Wurm, each added a case of his own in the period from 1927 to 1928. This makes a total of eighteen, including the case reported now.

More than three fourths of the cases reported occurred in males. In about one fourth of the cases the organism which was recovered was Str. haemolyticus.

DISCUSSION

WILLIAM C. VON GLAHN: Several years ago I observed a somewhat similar case of suppurative lymphangitis of the thoracic duct, the cause of infection being an abrasion of the left thigh. The organism in that case was also Str. haemolyticus.

MULTIPLE ANEURYSMS, PROBABLY SYPHILITIC, ASSOCIATED WITH RHEUMATIC CARDITIS. A. ROTTINO and HENRY J. SPENCER (by invitation).

This report concerns itself with a remarkable case in which was found universal involvement of the arterial tree by medial necrosis and fibrosis with the formation of numerous dilatations or aneurysms.

Though the literature was reviewed for forty years back, no similar report was discovered.

A 49 year old woman entered Bellevue Hospital with progressive dyspnea, weakness and loss of vision beginning insidiously six months before. A history of syphilis and rheumatism was absent. Besides signs of congestive failure, pulsating aneurysms in the neck, upper and lower extremities and aorta were found. Weakness was the prominent symptom. Death occurred in seventy days.

At necropsy the heart and arterial tree were of principal interest. In addition to cardiac hypertrophy there were thickening of a few chordae tendineae and small aneurysms at the closing margins of the aortic and mitral valves. The ascending aorta was transformed into an aneurysm with its walls thickened in places and thinned in others. Linear wrinklings, irregular scars and raised hyaline plaques affected the intima not only of the entire aorta but also of the pulmonary and all other arteries throughout the body. The aneurysms seen clinically were dilatations of thinned vessels of the neck, of the abdominal viscera and of both extremities. Aneurysms were found also affecting the ophthalmic arteries.

The microscopic lesion consisted of a medial necrosis destroying in a wholesale manner the elastic lamellae. There were extensive areas of replacement fibrosis associated with vascularization and round cell infiltration. In the intima fibrous plaques of varying sizes and thicknesses had formed. The vasa vasorum in the adventitia had thick walls and narrow lumens. The aforementioned changes were seen in all vessels described grossly as changed. Active valvulitis without verrucae was seen in the mitral valve. Aschoff bodies were found in the myocardium.

From the gross and microscopic appearance of the aortic lesions one would be entirely justified in ascribing the disease to syphilis. One might, however, raise an objection, since it is unusual to see such extensive involvement in this disease. To explain the aneurysms of the aortic and mitral valves on the same basis would be running counter to the opinion that syphilis does not attack valves primarily. The presence of the rheumatic type of lesion may well be a coincidence. If it has a meaning, this must for the present remain obscure.

DISCUSSION

ANDREA SACCONE: I should like to ask whether the blood cholesterol was studied in this case, and whether sections have been stained for fat, because I encountered a case of multiple aneurysms in a girl of 18 years in which cholesterol was found in the intima of the arteries, more or less diffuse; so that in cases of this type the disturbance in the metabolism of cholesterol must be considered, and I think it is important to make a cholesterol determination.

S. H. POLAYES: Was mention made of spirochetal studies?

A. ROTTINO: Though sections were stained by the Levaditi method, we were unable to demonstrate the presence of spirochetes.

A study of the cholesterol metabolism was not made clinically. The sections showed no cholesterol crystals. Preparations stained with scarlet red and sudan III revealed little or no fat in the aorta.

THE VISCERAL PATHOLOGY IN SCARLET FEVER. HENRY BRODY (by invitation) and LAWRENCE W. SMITH.

This is a study of sixty-one autopsies in cases from the Willard Parker Hospital, the Department of Hospitals, New York, forty-five of which were definitely cases of scarlet fever, the remainder probably so. In this paper is presented a

study only of the nonlocal visceral lesions, a detailed discussion of the cardiac pathology being omitted.

Nonsuppurative, toxic complications of scarlet fever, particularly in the kidney and liver, have long been recognized by the clinician. The underlying pathologic picture has been particularly well described for the kidney and for other viscera. We have been especially impressed, in this study, with the frequency with which a certain type of lesion occurs in the various organs from persons dying of scarlet fever. Extensive lesions of the type to be described, the indubitable immediate cause of death, have not been frequent, but the somewhat less extensive and early lesions are common. The lesion is an interstitial one, consisting of an exudate mainly of round cells. These cannot be said to be of one type. Perhaps, by and large, lymphocytes predominate. Plasma cells are numerous. Other types of less easily classified round cells occur in considerable numbers. Giant cells are practically absent. Polymorphonuclears occur, but for the most part in small numbers, and few of these are eosinophils. The lesion has been found in almost all of the body tissues. The exact nature varies with the location. This is consequent on the fact that the interstitial nature of the lesion is not primary. It is not, we believe, the result of direct injury to interstitial tissue by the local action of metastatic streptococci or by a blood-borne bacterial toxin. We feel that it represents, primarily, a widespread injury to vascular endothelium with secondary development of fluid and cellular exudation.

All the available material at the Willard Parker Hospital from all of the autopsies on patients dying of scarlet fever or whose condition was suspected of being scarlet fever is presented. In addition, a number of cases of streptococcic infection, either primary or secondary, were also studied for comparative purposes. The material available for study was the routine autopsy sections. These had been fixed in Zenker's fluid and stained with tetra-brom-di-chlorfluorescein plus methylene blue, the routine laboratory stain. A description of the lesions found in the various organs follows:

Heart.—Cardiac lesions of varying severity occur in over 90 per cent of the cases. These fall into three overlapping types: (1) either a focal or a diffuse interstitial infiltration by mononuclear cells, having no apparent distribution with reference to the cardiac blood vessels. This type is rare except as it occurs with either of the next two; (2) an infiltration in or about the smaller coronary arteries, taking the form of an arteritis or a periarteritis, in which the invading cells are mononuclear, although in some cases there occurs an admixture of polymorphonuclears, some of which occasionally are eosinophils; (3) the commonest finding, consisting of an infiltration beneath the endothelium of coronary veins, the endocardium or the endothelium of the thebesian vessels.

Kidney.—The kidney is both congested and edematous and shows marked tubular degeneration. The outstanding lesion is interstitial nephritis. This consists primarily of a mononuclear interstitial exudate in the boundary zone between the cortex and the medulla. Possibly, as Schridde suggested, there is a preinfiltrative stage with accumulations of numbers of mononuclear cells in the tubular capillaries. The earliest certainly recognizable lesion is an accumulation of numbers of cells about the long veins of the boundary zone without any interstitial infiltration. More extensive lesions definitely appear to spread from these sites. Secondary foci occur, for the most part, beneath the capsule and occasionally beneath the pelvic epithelium. In the very extensive conditions the picture resembles, both grossly and microscopically, lymphatic leukemia.

Adrenal.—The adrenal is almost always congested, the medulla more markedly than the cortex. Hemorrhage occurs. Cortical granular degeneration is frequent. Again, to us the striking change is an infiltration of the walls of the medullary venous sinuses by mononuclear cells, spreading to a degree through the medulla. This infiltration rarely spreads into the zona reticularis, though a case with diffuse, though not intense, cortical involvement was seen.

Liver.—The liver is markedly congested and frequently shows central fatty degeneration. Edema, often extreme, is usually present. Again, mononuclear interstitial infiltration in the portal region occurs, and in many cases this appears to be definitely derived from the portal veins and their capillary branches.

Spleen.—Acute splenic tumor is common. Microscopically, there are congestion and edema, with widely distended sinusoids, containing few polymorphonuclear cells. The splenic follicles are either hyperplastic or show necrotic centers. Again, infiltration of the vein and sinusoidal walls is prominent.

Other Organs.—Similar lesions about veins and capillaries have been seen in the pancreas, lung, pituitary, testis, tissues of the pharynx, regional and distant lymph nodes, salivary glands and aorta.

Bacteria are not found associated with these lesions, although the blood culture is most frequently positive. It is believed that the picture represents a reaction to a circulating bacterial toxin, acting primarily on vascular endothelium.

DISCUSSION

PAUL KLEMPERER: How often did you find thrombosis in the smaller or larger blood vessels?

HENRY BRODY: It was very infrequent.

ALFRED PLAUT: Were there any necrotic changes in the walls of the vessels, or deposits under the intima?

HENRY BRODY: I do not think we ever saw necrotic changes in the walls of the vessels. We may occasionally have seen hyaline changes, but these were not particularly associated with the lesion.

ALFRED PLAUT: I asked that question because I have seen in a young child whose age I do not recall a general inflammatory infiltration nearly identical with those you showed, but in the case of which I speak there were multiple necrotizing arterial lesions. It was not a case of scarlet fever.

MENDEL JACOBI: I noted that Dr. Brody seemed to stay away from the question of hemorrhages. He casually mentioned that hemorrhages in the adrenal occurred. Some years ago I examined some cases of scarlet fever post mortem, though I did not study them to the extent that Dr. Brody examined his, and in association with these lesions I noticed in the kidney and liver frequent hemorrhages, petechial in character. I could not find thromboses except in isolated instances. I should like to ask whether a study was made in regard to the frequency of hemorrhages, and what happened to the elastic tissue in these various vessels.

HENRY BRODY: We were rather surprised to find that hemorrhage occurred as infrequently as it did. We found hemorrhage in the adrenal oftener than in any other organ; perhaps it was present in less than 10 per cent of our cases. I have only seen it once in the kidney. In the literature adrenal hemorrhage is described as a complication of scarlet fever.

We have not studied the walls of the vessels in detail.

PATHOLOGY OF B VIRUS INFECTION. ALBERT B. SABIN (by invitation).

The B virus was isolated from the spinal cord and spleen of a human being with acute ascending transverse myelitis which followed the bite of an apparently normal rhesus monkey. The human lesions attributable to the virus included necrotic vesiculopustular lesions on the fingers at the bitten sites, necrotic foci in the regional lymph nodes and spleen, widespread necrosis in the adrenals and lesions in the central nervous system involving chiefly the spinal cord and medulla.

The B virus can be distinguished from all known viruses by its biologic and immunologic properties. It is pathogenic for rabbits, rhesus monkeys and, to a lesser degree, for guinea-pigs and mice. There is some evidence that it is indigenous to rhesus monkeys.

In the rhesus monkey the B virus produces lesions characterized by proliferation, the formation of acidophilic intranuclear inclusions and later cellular necrosis and inflammatory reaction. Lesions can probably develop in every tissue or organ, but under the experimental conditions of this study they were observed in the skin, peritoneum and omentum, liver, spleen, adrenals, ovaries, lymph nodes and nervous system. Prominent among the lesions is specific necrosis of the blood vessels. Intravenous inoculation of the virus gives rise to an exanthem and an enanthem. Intracerebral inoculation is rapidly fatal, while after peripheral inoculation there are no signs of an involvement of the central nervous system and the animals survive. The disease in the rabbit is similar to that in the monkey except that adhesive peritonitis does not follow intraperitoneal inoculation, and peripheral inoculation leads to constant ascending infection of the nerve axis.

PATHOLOGY OF GIANT TUBERCULOUS CAVITIES. LEWIS E. SILTZBACH (by invitation).

Eleven instances of complete cavernous destruction of a tuberculous lung were studied. Such lungs show either a single enormous cavity extending from apex to base or complete cavitation of each lobe with persistence of the intervening interlobar adhesion. The lung is generally markedly shrunken and is surrounded by dense fibrous pleural adhesions. The opposite lung contains relatively fresh tuberculous lesions occupying limited areas. In all eleven instances the process of complete cavitation was left-sided and occurred exclusively in females. In the literature nine clinical reports of cases of this form of pulmonary tuberculosis, with one exception, record involvement of the left lung. Two lungs showing complete cavernous destruction were examined microscopically in their entirety. In the microscopic remains of the collapse-indurated parenchyma, which were present only at the base of the cavity, innumerable lymphocytic nodular aggregates as well as a few scattered miliary tubercles were found. A surprisingly large number of small encapsulated caseous and calcified nodules of old caseous pneumonia and caseous bronchitis were also observed. Many of these old lesions showed reactivation of the tuberculous process as well as erosion and discharge into the lumen of the cavity.

The cavity is lined by nonspecific granulation tissue, and the wall of the cavity only rarely contains evidence of tuberculous change. Areas were encountered where no definitely formed wall of a cavity was present, and here the remains of lung tissue or even the fibrous pleural adhesion lay bare in the lumen of the cavity, undergoing severe nontuberculous purulent necrosis. The dense fibrous tissue of the pleural adhesion showed a rich network of elastic fibrils, probably originating in response to the forces of respiratory movements. The tracheobronchial lymph nodes contained numerous fresh tubercles as well as old and encapsulated caseated and calcified foci.

Regular Meeting, April 25, 1935

WILLIAM C. VON GLAHN, *President, in the Chair*

IRVING GRAEF, *Secretary*

SPINDLE CELL SARCOMA ARISING IN A FISTULOUS TRACT. SOLOMON WEINTRAUB and (by invitation) JOSEPH G. LEVY.

The following report is of interest because of the rarity of the condition, the unusual location of the primary tumor, and the question of etiology.

A colored man, aged 40, single, a chauffeur, was admitted to Harlem Hospital on Feb. 26, 1935, for discharging sinuses about the rectum with old perianal tracts.

In the spring of 1934 the patient noticed a small "pimple" near the anal orifice, which he opened several times with a sterilized needle. Following this he had a succession of small "boils" in the perianal region which opened and left discharging sinuses surrounding the posterior commissure of the rectum.

In November 1934 he was operated on for a horseshoe-shaped fistula. The internal opening was not found at that time, but the tracts around the rectum were dissected out. He returned for dressings, and on several occasions the surgeon was said to have removed "proud flesh" from the site of the operation.

His parents are living and well, and ten brothers and four sisters are all alive and in apparent good health.

On examination the local area presented granulating tissue and discharging sinuses on both sides of the rectum. Four days later he was operated on. The internal opening of the fistula was located and the usual operation performed. The postoperative course was uneventful, and the man left the hospital in ten days apparently cured. He was to return for dressings. It was noticed that the areas of operation were gradually filling up with what appeared to be exuberant granulation tissue. This tissue in five weeks grew from a flat elevated tissue to a cauliflower-like mass about the size of an orange. He was then rehospitalized.

During the interval between the two admissions the patient felt well; he had no loss of weight, no tenesmus, no obstructive symptoms and no bleeding but complained of the discomfort from the presence of the mass on sitting and walking.

Digital and proctoscopic examination revealed no ulceration or other changes of the rectal mucosa and no internal masses. There were no enlarged glands. The external mass was elliptic and measured 11.5 by 6.2 cm. It was covered by crusts of dry exudate and appeared to arise from the area of the dissected tract, following exactly the lines of incision in the left perianal region, crossing the posterior commissure, and then continuing for a short distance on to the right side.

Biopsies were taken from five different areas of the tumor. Roentgen examination of the bones of the pelvis, both shoulders and the chest showed no abnormalities. The Kahn and Frei tests were negative.

Microscopic examination showed a large collection of spindle-shaped cells conforming in all respects to the spindle-shaped cells seen in sarcoma. There were collections of small round cells and a few polymorphonuclear cells, showing secondary inflammatory invasion.

We could find only two references in the literature to sarcoma arising from fistulous tracts, that is, if we disregard the usual rectal and anal sarcomas. Malherbe recorded "sarcoma of the ischiorectal fossa in a woman of 50 with also a primary sarcoma of the buttocks."

The etiology of this primary sarcoma raises the question whether the tumor arose from the granulation tissue or directly from fistulous tracts that had undergone malignant changes, or whether inflammation was an etiologic factor in the lesion. Dr. James Ewing treats this question as follows: "Many clinical observations point to the development of sarcoma from granulation tissue. It seems highly probable also that sarcoma, like carcinoma, arises through exaggerated inflammation and regeneration overgrowth of tissue cells."

DISCUSSION

LIONEL S. AUSTER: Were further biopsies made on tissue taken from different areas, and is there any roentgen evidence of the site of origin?

JOSEPH G. LEVY: Biopsies were made on specimens taken from three different sections of the tumor, but no x-ray picture to find out the origin was taken, only one to determine whether these were metastases. It appears as if it arose entirely from the fistulous tract. The tumor surrounds the anal orifice on the left side, goes around the posterior commissure and down on the right side where the tracts were excised. I wonder if in any way the fistulas were the etiologic agent.

LIONEL S. AUSTER: That brings out the question I had in mind. Every once in a while there have been reported in the literature instances of so-called sarcoma

of the skin in which on closer examination of the picture or the slides one can definitely demonstrate that the tumors are epithelial growths which have taken on a somewhat spindle-celled appearance. In some of them there has been evidence of histogenesis from the basal layer. They look like spindle-cell sarcoma, but in some areas there is a definite epithelial structure, and in view of the fact that this patient had sinus tracts, the tumor might have originated in the lining of one of these, stimulated by the infection and trauma.

SOLOMON WEINTRAUB: I think the epithelial-like cells which are present here really represent a secondary infection. A number of round cells can be seen in the microscopic slide, but there is no evidence of this in the photograph. There was a superimposed infection.

METHODS OF GRADING MAMMARY CARCINOMA COMPARED WITH THE CLINICAL OUTCOME. LAWRENCE SOPHIAN (by invitation).

All records of cases of carcinoma of the female breast at Roosevelt Hospital in which a radical operation had been done and a clinical follow-up of ten years or longer was available were analyzed histologically. There were 124 such cases. Examination revealed that 69 per cent of the patients had metastatic involvement of axillary nodes at the time of operation. Following the example of Haagensen, I graded the cases separately by growth characteristics: size of nuclei, variability in nuclei as to shape and size, adenoid arrangement, frequency of mitosis, presence of secretion, degree of fibrosis and hyalinization, and number of lymphocytes invading the tumor. When papillary formation, comedo type of growth or gelatinous degeneration was present note was made of it. Each factor mentioned was in each case given a number, 1, 2 or 3, indicating the degree of departure from normal and, presumably, the degree of malignancy. The size and shape of the nuclei were determined comparatively by making camera lucida drawings under a magnification of 400 times for each slide. The nuclei were thought to be more sharply outlined and less subject to artefact than the cytoplasm. Small nuclei were graded 1 and large ones 3. Those of uniform shape and size, whatever their size, were likewise graded 1 as to variability. Departures from this constancy were graded 2 and 3. Adenoid arrangement was accorded only two grades since well formed and constant gland formation was rarely found. The frequent, although inconstant, presence of adenoid structure was graded 1-2 and the absence of adenoid structure 3.

Secretion was estimated by vacuolation and clarity of cytoplasm, and its presence was noted by a grade of 1 if abundant and 2 if moderate in amount.

Mitoses were roughly counted by high power fields. If several were present in each field grade 3 was given. If a mitosis was found in practically every field the grade was called 2, and if there was difficulty in finding any mitoses the grade was called 1.

Fibrosis was graded 1 if abundant, with hyalinization present, and 3 if scanty and without hyalinization. Lymphocytic infiltration was graded 1 if abundant and 3 if scanty, in view of the theory of MacCarty that these are defensive factors.

These comparisons brought out the following facts: The percentage of axillary metastases was definitely higher in grade 3 than in grade 1 in regard to nuclear size, nuclear variability, secretion, adenoid arrangement, number of mitoses and lymphocytic infiltration. The greatest variation was in the grading by adenoid arrangement, in which almost twice as great an incidence of axillary metastases was found in the group of carcinoma simplex as in that of adenocarcinoma.

In the relatively homogeneous group of cases without axillary metastases there were a higher percentage of living patients and a longer span of life for the patients who died in the group graded 1 than in the group graded 3 in regard to nuclear size, nuclear variability, adenoid arrangement, secretion, mitosis and lymphocytic infiltration. The grading by fibrosis showed the most favorable cases in grade 3.

In order to combine the factors found useful in grading, the total grade was obtained by adding the individual grades together for the four major criteria—nuclear size, nuclear variability, adenoid arrangement and mitotic frequency. Since these could each range from 1 to 3 the totals could range from 4 to 12. Favorable

factors such as abundant secretion or papillary arrangement or comedo formation were given some weight by reducing the total by 1 for each such factor. The total grade was then given as 1 when the sum of all factors was less than 7, as 2 when the sum was from 7 to 9, and as 3 when it was 10 or more. When the clinical cures in the 124 cases followed ten years or longer were charted by these groups it was found that 34 per cent of the patients in the grade 1 group were alive at the end of the period as against 19 per cent of those in the grade 2 group and 13 per cent of those in the grade 3 group. The influence of the presence of more cases in which there were no axillary metastases in the grade 1 group is seen if only the cases in which there were axillary metastases at the time of operation were charted. After ten years only 7 per cent of the patients were alive in each of the three grades. The length of life was, however, greater in the group with grade 1 carcinoma than in that with grade 2, and in that with grade 2 than in that with grade 3.

The importance of grading, therefore, is greatest in determining the prognosis for cases without axillary metastases. The favorable influence of adenoid arrangement on clinical outcome is due to the relative infrequency of axillary metastases at the time of operation in this group.

DISCUSSION

ROBERT CHAMBERS: What is the relation between nuclear size in these various grades of tumors and that in the normal mammary gland? In connection with the deaths due to metastases, is there any regularity as to where metastases occur?

IRVING GRAEF: Were any of these patients treated with radiation before operation?

LAWRENCE SOPHIAN: The grade 1 size of the nucleus corresponds to the size of the normal nucleus of the epithelium of the mammary gland.

ROBERT CHAMBERS: That is the largest?

LAWRENCE SOPHIAN: No, it is the smallest. I took it merely according to what had previously been written, that large cells are thought to be abnormal and more malignant, and that small cells belong to grade 1. These nuclei are between 4 and 6 microns in diameter and are about the size of the normal mammary epithelial nuclei. As far as the presence of metastases in various parts in the fatal cases goes, I did not have a high enough percentage of autopsies to make a reasonable estimate, but clinically the greatest occurrence of metastases was in the pleura, the second greatest was in the liver, and the third was in the bones.

None of these patients received preoperative radiation; some received postoperative radiation.

STUDIES OF MELANOMA IN TISSUE CULTURE. ROBERT CHAMBERS (by invitation).

During the past year my associate, C. G. Grand, and I have been making a study of mouse melanoma in tissue culture, an excellent method for use in the identification of the various types of cells found in this tumor, as the cells migrate from the margin of the explant and retain their specific morphology.

Fragments of the tumor tend to impart an alkaline reaction to the culture medium. This alkalinity has an inhibitory effect on the tumor. However, the presence of any *growing* tissue in the vicinity neutralizes the alkalinity, whereupon the cells of the tumor migrate and proliferate.

Macrophages.—These are the first cells to migrate in large numbers and are heavily laden with pigment which, under high magnification, can be seen to be in the form of irregularly sized granules and clumps of granules. The phagocytic activity of these cells continues as long as they are alive, and they readily ingest carmine granules placed in the medium even when they seem to be filled with melanin granules. They have never been seen to lose their granules except on disintegration.

Fibrocytes.—In a thirty-six hour culture in which out-wandering of cells is evident the fibrocytes begin to be seen. They always appear later than the macrophages. The fibrocytes, even when first seen, contain a dense mass of melanin granules clustered about the nucleus in the main cell body. The granules are seldom, if ever, in the extended cell processes.

Melanoblasts.—These dendritic cells have never been seen in cultures earlier than forty-eight, and usually appear only later than seventy-two, hours after implantation. The first sign of their appearance is the extension of delicate filamentous processes from the margin of the explant. The time taken for the cell body to appear is usually a matter of several days after the processes first come into evidence. This excessively slow migratory movement is a characteristic which is maintained even after the melanoblasts have migrated into the medium. The processes are very slender and long and are frequently branched. Melanin granules are mainly in the periphery of the cell body and in the dendrites, where they tend to be collected in irregular swellings giving the dendrites a varicose appearance. The constrictions between some of the swellings are very pronounced. The irregularity in size and the clumped state of the granules in the heavily pigmented melanoblasts are not to be confused with their condition of irregularity in phagocytes and fibrocytes, in which the apparent agglutination is throughout the entire cell.

In the hundreds of mouse and in the few human melanoma cultures which have been grown in this laboratory we have never observed cells which even remotely may be identified with epithelium. All these cultures have shown a rich supply of connective tissue elements with numerous spindle-shaped fibrocytes. The experimental evidence included in this paper confirms the generally accepted opinion that the dendritic melanoblasts elaborate, while the other cells of the tumor, particularly the macrophages, ingest, melanin.

An account of this work appeared in the May 1935 issue of the *American Journal of Cancer*, p. 36.

DISCUSSION

JACOB FURTH: Could you make successive passages of the melanoma cultures and reimplant them into mice? Do macrophages perform the same rôle as fibroblasts in making the explant less alkaline, thus preparing it for the growth of melanoblasts? Do the macrophages come from the parenchyma of the tumor or from the blood vessels?

ROBERT CHAMBERS: In the case of implantation, that is the usual procedure for maintaining our material. The culture can be grown for weeks and then be planted back into a mouse where it produces tumor growth.

Growing cultures of macrophages will acidify the medium, having an action similar to that of the fibrocytes. We have had cultures of the buffy coat of blood planted with a melanoma, and the cells which grew from it, the monocytes, rapidly proliferated and acidified the medium.

The question of the source of macrophages is a moot point. They may originate from the blood vessels, but they are found in quantities in the interstices of many tissues, and in all our tumors we have had more macrophages than any other kind of wandering cells. In our cultures of kidney, which has a rich supply of blood vessels, very few macrophages appear, but plenty of fibrocytes, while in tumor cultures with relatively few blood vessels we always have an abundance of macrophages.

DIFFUSE SARCOMA OF THE ENDOMETRIUM: REPORT OF A CASE. LOUISE H. MEEKER and G. L. MOENCH.

Endometrial sarcoma is divided into the more frequent circumscribed and the rarer diffuse type. The case we report is an example of the diffuse type involving the entire endometrium.

The surgically removed specimen was a uterus (including the cervix and with both tubes and ovaries attached). It was 100 mm. in length and 35 by 40 mm.

in diameter at the cervical end. At the fundus it measured approximately 42 by 35 mm. It had been split open, disclosing a uterine canal lined by an irregularly thickened endometrium 20 mm. in thickness in some areas. The superficial portions were gray-green, apparently largely necrotic and infiltrated by purulent exudate. In the deeper portion there was a gray opaque layer about 5 mm. in thickness which poorly demarcated the involved endometrium from the underlying myometrium. Microscopically the neoplastic tissue was formed by an edematous diffuse proliferation of somewhat irregular cells containing large nuclei with abundant mitotic figures. The cells, which often formed poorly defined irregular nests, were spindle-shaped in some places and in others presented multiple branches which extended to the neighboring cells. There were no endometrial glands at any point, and epithelial cells were not recognized.

The manner of diffuse growth and the type of the neoplastic cells warrant a diagnosis of diffuse round cell and spindle cell sarcoma arising from the connective tissue of the endometrium.

DISCUSSION

LAWRENCE SOPHIAN: I am somewhat familiar with the subject of sarcoma of the endometrium because about five years ago in the laboratory of Roosevelt Hospital we had two cases within about ten months of each other both of which were of mixed cell types; that is, there were irregular groups of endometrial glands embedded in tumor in which the cells were of extraordinary size, and there was also evidence of a possible teratomatous origin, i. e., foci of cartilage and possibly some striated muscle. This is the type of tumor which Wilfred Shaw described; it is the type called botryoid sarcoma, and occurs most frequently in young women and second most frequently in women past 50, beyond the menopause; both of our patients were in the late 50's, and I think that in this respect the cases correspond to the case of Dr. Meeker, with the difference that in these sections I see a pure type of growth rather than mixed types. I think possibly the origin is similar, but in these sections the overgrowth of the more immature spindle cell has reduced the structure to an apparently single cell type. Both of the patients at the Roosevelt Hospital survived the operation but died of recurrence or of metastases within the subsequent two year period.

Book Reviews

Röntgenbefund und pathologisch-anatomischer Befund bei Lungenkrankheiten. Versuch einer kritischen Vergleichung. By Dr. med. Max Versé, o.ö. Professor der allgemeinen Pathologie und pathologischen Anatomie, Direktor des pathologischen Instituts der Universität Marburg. Price, 18 marks. Volume 1, text. Pp. 96. Volume 2, atlas, with 144 illustrations. Berlin: Otto Elsner Verlagsgesellschaft, 1935.

The purpose of this work was to study roentgenograms of the lungs in comparison with their gross appearance in diseases with marked structural alterations. Under the most favorable conditions roentgenograms were made of the lungs, which were then cut into suitable sections after hardening, and the results of the two methods compared carefully. In a number of cases roentgenograms of the lungs during life were available for comparison also. The study includes fifty-four cases in all, illustrating the various forms of atelectasis, local circulatory disturbances, inflammatory processes, tuberculous disease (primary complex, infraclavicular foci, acute disseminations), Hodgkin's disease and neoplasms. The first volume contains the text, in which the cases and the illustrations are described and summarized according to groups. The second volume contains one hundred and forty-four full-page illustrations on special paper, each with a brief legend. In most cases the roentgenogram is reproduced on one page and the photograph of the gross appearance of the cut surface on the opposite page. All the reproductions are good. Frequently the lung is shown roentgenographically in both the more or less collapsed and the fully distended state. With the text in one volume and the illustrations in the other, careful comparative study is facilitated. The book will be of interest to all who are concerned in the roentgen examination of the lungs. It illustrates well the advantages that result from cooperation between the roentgenologist and the pathologico-anatomist. The prediction is ventured that Versé will be followed by more ambitious attempts along the same lines.

Repertorio sistematico dei miceti dell'uomo e degli animali. By Arturo Nannizzi. Price, 100 lire. Pp. 556. Siena: s. a. poligr. Meini, 1934.

There has long been a need for a catalog of the species of fungi. Mycology is one of the least well known fields in medicine, and when the pathologist essays to determine a species he is generally at a loss as to sources of information. Nannizzi's catalog, a 557 page volume in Italian printed on enamel paper and abundantly illustrated with first class reproductions, fills this want. The diagnosis of each species is recorded in a paragraph, worded in telegraphic style, which avoids unnecessary wading through Italian verbiage. While this language is not at the command of most American physicians, their knowledge of Latin and of general mycologic terms ease the situation and make the information readily available with only occasional use of the Italian dictionary. Unfortunately, references are not included.